SLEEP APNEA ACTIVITY AND ITS CONCOMITANTS IN A SUBCLINICAL POPULATION

By

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Sleep Apnea Syndrome (SAS) is a nocturnal respiratory disorder with serious consequences. Patients with SAS experience apneas (pauses in breathing of 10 or more seconds) and hypopneas (declines in the amplitude of breathing accompanied by oxygen desaturation) while asleep. Recently, it has become apparent that apneas and hypopneas may occur in otherwise apparently normal subjects. A sample selected to display a wide range of sleep disordered breathing (heavy snoring males in good health and over 30 years of age) received detailed measurement of their nocturnal respiration, sleep, cognitive skills, and health in an attempt to clarify the impact of apneas and hypopneas in a subclinical population.

Forty-six heavy snoring males in good health with a mean age of 50 years and a mean weight of 190 pounds comprised the sample. During an experimental evening they

received testing and filled out various questionnaires before sleeping overnight with their sleep and breathing continuously recorded. Sixty-two per cent of these subjects experienced at least one event, while 13% had more than 5 events per hour of sleep. Most events occurred in light slow wave or REM sleep and were linked to obesity. Subjects with high levels of apnea/hypopnea (more than 5 per hour) experienced significantly exacerbated oxygen desaturation relative to the remaining subjects. Oxygen desaturation was linked to higher blood pressure readings. A typical "first night" effect on the sleep of the subjects in the lab was noted, resulting in a lighter sleep than usual and obscuring possible relationships between sleep and respiratory events, which were not observed. Deteriorating overnight respiratory indices were associated with increased sleepiness and napping. High levels of apnea/hypopnea were associated with declining scores on tests measuring non-verbal intelligence, verbal and non-verbal memory, expressive verbal fluency, and cognitive flexibility. It is speculated that hypoxia induced changes in cerebral cholinergic synthetic pathways underlie these changes.

It is concluded that a significant subgroup of heavy snoring males who experience multiple apnea/hypopneas are at increased risk of significant oxygen desaturation, daytime sleepiness, and cognitive changes. This group may fall on a continuum with sleep apnea syndrome patients.

CHAPTER ONE
INTRODUCTION

Sleep apneas are respiratory pauses during sleep. According to the Association of Sleep Disorders Centers Nosology of Sleep Disorders (ASDC, 1979), a sleep apnea syndrome (SAS) is a potentially lethal condition characterized by multiple apneas, excessive daytime sleepiness, alterations of consciousness, and cardiopulmonary complications. The apnea episodes are thought to be the causal factor behind the other deficits associated with SAS (Guilleminault et al., 1978).

Polysomnographic recordings in various populations have revealed the occurrence of sleep apneas in the general population, and particularly in aging populations. Estimates of the prevalence of at least a few sleep apneas in older subjects have ranged as high as 75% (Carskadon and Dement, 1981b). Carskadon et al. (1980) have suggested that sleep apneas in older subjects may be implicated in insomnia, cardiac ailments, and even senility.

However, certain reports have documented the presence of multiple sleep apnea episodes in subjects without apparent pathology (Orr et al., 1979). This evidence obscures the role of sleep apneas in the other pathologies

noted in SAS patients. The link between apneas and pathology may be more complex than was originally thought, given its apparently benign occurrence in otherwise asymptomatic subjects.

The present study will examine the correlates of sleep apnea episodes in a population selected to display a wide range of such events. The relationship between sleep apnea indices and sleep characteristics, age, weight and a variety of deficit measurements will be analyzed.

A review of the current data available on various aspects of sleep apneas and sleep apnea syndromes will be presented as background for the study. The diagnosis, history, incidence, and characteristics of sleep apneas and sleep apnea syndrome will be reviewed, followed by a discussion of variables associated with sleep apneas. Lastly, the deficits commonly found in sleep apnea syndrome will be detailed, along with measurements thought to be sensitive to these deficits.

Definitions and Terminology

Sleep apneas have been defined as cessations of airflow at the mouth and nose which last for 10 or more seconds (Guilleminault et al., 1976). In a sleep apnea syndrome (SAS), multiple sleep apneas are accompanied by snoring, excessive daytime sleepiness, cardiopulmonary complications, and altered states of consciousness. The ease of quantification of sleep apneas has led to their use as an important tool in diagnosing SAS. Guilleminault

et al. (1976) first suggested that the occurrence of 30 or more apneas in 7 or more hours of sleep was diagnostic of SAS, while Guilleminault et al. (1978) proposed the use of an apnea index (AI; number of apneas/number of hours sleep) in excess of 5 as a cut-off score to diagnose the syndrome. Later, Carskadon et al. (1980) combined apneas and hypopneas (a reduction in airflow of 50% or more at the mouth and nose) to form an apnea + hypopnea index (AHI) with 5 utilized as a diagnostic level of sleep apnea syndrome. As can be appreciated from the preceding discussion, the diagnostic criteria for SAS have undergone a rapid evolution, with remarkably little validation work published.

History and Characteristics of Sleep Apnea Syndrome

Sleep Apnea Syndrome falls within the larger category of Sleep Disordered Breathing (Block, 1980). Respiratory disorders within this category involve changes in breathing patterns during sleep. Syndromes described within this category include Pickwickian Syndrome; Sleep Apnea Syndrome; Chronic Obstructive Lung Disease; and syndromes of Primary and Secondary Alveolar Hypoventilation (Block, 1980; Guilleminault et al., 1976).

The first disorder described in this group was the Pickwickian Syndrome. These patients were initially identified by a chronic daytime hypersomnolence, obesity, Cheyne-Stokes breathing, hypercapnia and hypoxemia. This

syndrome typically results in complications such as right sided congestive heart failure, pulmonary hypertension, and peripheral edema (Block, 1980). An exacerbation of disordered breathing (apnea) as well as hypercapnia and hypoxemia (often severe) occurs with sleep onset. Treatment consists of oxygen therapy, respiratory stimulants, and maintenance of wakefulness.

The discovery of a sleep induced exacerbation of the symptoms accompanying Pickwickian Syndrome spurred a systematic investigation of sleep respiratory events (Gastaut et al., 1965). The new emphasis on noctural respiration led to a series of investigations which documented sleep induced respiratory dysrhythmias in non-obese subjects (Lugarasi et al., 1968). A new group of sleep disordered breathers designated as Sleep Apnea Syndrome emerged, with several features which distinguished them from Pickwickians. Among these differences were weight (i.e., SAS patients were not necessarily obese), daytime respiratory control (i.e., SAS patients were typically not hypercapnic during waking as were Pickwickians), sex (i.e., while 40% of Pickwickians were female, very few premenapausal females have been identified with SAS), and age (i.e, SAS patients are typically younger than Pickwickians)(Block, 1980).

Two large samples of SAS patients have been reported in the literature, allowing characterization of typical SAS patients. Guilleminault et al. (1978) reported on a

series of 50 patients diagnosed with SAS over a period of six years. Age ranged from 28-62 with a mean age of 45.5. The sample consisted of 48 males and 2 females. Thirty-nine were referred on the basis of excessive daytime sleepiness, while 7 were referred for loud snoring and abnormal movements reported by their spouses. Sixty percent of the patients were more than 15% above ideal weight. Other symptoms included hypnagogic hallucinations, automatic behaviors, intellectual deterioration, personality changes, impotence, morning headaches, and hypertension. Weitzman, Kahn and Pollak (1980) report data on a group of 10 SAS patients seen in their clinic. These subjects displayed the following characteristics: age between 38 and 47, obesity, male sex, nicotine dependence, hypertension, complaints of excessive daytime sleepiness, and the presence of serious cardiac arrhythmias. (This group was selected from a larger sample of 38 patients.) Thus, pathological symptomatology associated with a diagnosed SAS include excessive daytime somnolence, cardiopulmonary complications and cognitive/intellectual changes; a "typical" SAS patient is a middle aged male who snores and is obese.

Incidence of Sleep Apnea Activity

The incidence of sleep apnea activity and sleep apnea syndrome have been frequently confused. While sleep apneas have been an important diagnostic tool for identifying sleep apnea syndrome, they have not been

definitively demonstrated to be the necessary and sufficient cause of the syndrome. Thus, for the purposes of the following review, the focus will be on occurrence and level of sleep apnea activity in both sleep apnea syndrome subjects and other populations. The full range of sleep apnea activity will be reflected by noting the presence of sleep apnea activity, and an indication of the quantitative level of the activity will be presented in the apnea index (AI) or the apnea + hypopnea index (AHI). Recall that an AI of 5 has been frequently utilized as a cut-off score for identifying SAS patients.

A review of the literature suggests that at least three sampling strategies have been used for studying the incidence of sleep apnea activity. Subjects have been selected on the basis of one of the following three criteria: 1) absence of sleep or respiratory complaints, 2) presence of sleep or respiratory complaints, or 3) sampling without regard to these variables.

Because diagnosis of SAS is often dependent on number of sleep apneas (or level of SAA), most researchers report number of apneas observed, although some report only on number of subjects who exceed one of the criteria for SAS. A review of studies with samples of 20 or greater will be presented with careful note of the sampling strategy utilized, as well as the dependent measure of apnea.

One sampling strategy which has been pursued is to exclude subjects who complain of sleep or respiratory difficulties. Screening for sleep complaints varies widely. Guilleminault et al. (1978) studied a sample of 20 "normals" (presumably noncomplaining subjects). These subjects ranged in age from 40-60 years. Males showed a mean number of apneas of 7 (range 1-25), while females showed a mean number of apneas of 2 (range 0-5). Thus, none of these noncomplaining subjects presented a clinical syndrome of sleep apnea, although sleep apneas did occur apparently without pathology. Block et al. (1979) studied 49 subjects (M = 30, F = 19). Males in the sample had a mean age of 38, while females had a mean age of 29. Any potential subjects who complained of breathing difficulties or sleep disturbances were excluded from the study. Twelve males (40%) had episodes of sleep apnea while only 3 females (15%) suffered as well. For those subjects, males had a mean of 4.2 episodes, while females had a mean of 3. Within this sample, the number of apneas was not significantly correlated with increasing age, although occurrence of oxygen desaturation (a concomittant of disordered breathing) was positively correlated with age. Additionally, although the mean number of sleep apneas was not significantly different between sexes (M = 4.2, F = 3), the more sensitive measure of apneas with desaturation was (M = 3, F = 0). Webb (1974) studied 20 males with a mean age of 44. Subjects were excluded from

the study if they reported any "serious" sleep complaint. Two of the subjects reported consuming hypnotics for sleep induction, indicating that the criterion used in this study was less stringent than that of Block et al. (1979) report. Nine of the subjects (45%) suffered at least one episode of sleep apnea with a mean number of episodes of 2.5. All of the subjects with episodes of sleep apnea were older than the mean age of the sample, leading Webb to conclude that apnea is related to age. Bixler et al. (1982) constructed an age stratified patient representative sample of 100 subjects (M = 41, F = 59). In perhaps the most rigorous screening for sleep complaints in this group of studies, Bixler et al. eliminated any subject with a sleep complaint or chronic medication usage. For the entire sample, 6 males (14.6%) and 5 females (10.2%) had at least one episode of sleep apnea. For subjects under 30, 3.3%; for those between 30 and 50, 12.8%; and those 50-74, 19.4% suffered episodes of sleep apnea. For the subsample over 60, 25% had sleep apnea activity with 8.5 episodes for males and 10.5 episodes for females. In this sample, there was a nonsignificant trend toward more apnea activity in males and a significant positive correlation between age and sleep apnea.

Block et al. (1980) report data on 20 post menapausal women with a mean age of 59. Eight women (40%) had episodes of sleep apnea, with a mean number of episodes of

5. There was a significant correlation between apnea and age.

For noncomplaining subjects then, males suffer a higher incidence of apnea activity in virtually every study which compares sex effects. For males, incidences range widely from a low of 14.6% (Bixler et al., 1980) to a high of 45% (Webb, 1974); while females range from a low of 10.2% (Bixler et al., 1982) to a high of 40% (Block et al., 1980). These differences are probably due at least in part to age differences in male samples, as well as age differences in females (only as they reflect menapausal status). Reported number of apneas range from 2.5 (Webb, 1974) to 8.5 (Bixler et al., 1982) in males and from 2 (Guilleminault et al., 1978) to 10.5 (Bixler et al., 1982) in females. Many studies report a positive correlation between number of apneas and increasing age.

A second sampling technique which has been utilized has been studying subjects with sleep and breathing complaints. Kales et al. (1982) studied 200 subjects with primary complaints of insomnia. There were 82 males and 118 females in the sample with a mean age of 42.3. Sleep apnea activity was noted in 10.5% of this group (M = 13.4%, F = 8.5%) with a mean number of 11.2 episodes for males and 6.6 for females. Subjects with sleep apnea activity were significantly older (46.8) than those without (40.6). Ancoli-Israel et al. (1981) recruited 24 subjects whose answers to questionnaires provoked

suspicion of insomnia or nighttime breathing and muscular events. Eleven males ($\bar{x}$ = 72.5) and 13 females ($\bar{x}$ = 68.5) were studied. All of these subjects, save one male and one female, suffered at least one episode of sleep apnea. For those subjects with at least one episode of sleep apnea, males had a mean of 53 episodes of apnea, while females had a mean of 32 episodes. In contrast to the Kales et al. study, 6 males had a high level of sleep apnea (AI>5), while 3 females met this criterion. A relationship between age and apnea was not reported in this sample, possibly because of restricted range. These two studies of sleep disturbed subjects provide conflicting data. That is, the insomniac alone sample did not demonstrate an apnea incidence which was substantially different from a noncomplaining sample (10.5%), while the sample recruited for sleep induction, respiratory, and muscular differences showed very discrepant apnea incidences (nearly 100%). One potential explanation involves age, as the Ancoli-Israel sample is substantially older than Kales', although the aging samples have not reported this level of apnea before. An alternative explanation is that sampling insomniacs does not generate a high number of apneas, whereas aging sleep and respiratory disturbed subjects show a very high incidence of apnea. It would seem then that the relevant "complaint" would involve those reported by Ancoli-Israel et al. which are in addition to those noted by Kales et al. These are (as

nearly as can be judged) questions surrounding respiration.

The final category of incidence studies involves those which do not consider sleep complaints in their sampling. As in the other studies, these vary in their generalizability. Carskadon and Dement (1981b) recruited 40 aging subjects, including 18 males ($\bar{x}$ = 72.7) and 22 females ($\bar{x}$ = 74). Their exclusion criteria are somewhat problematic, involving excluding subjects who "spontaneously complain of sleep problems." Thus, it is unclear what this is a representative sample of, specifically whether the distribution of those not spontaneously complaining of sleep disturbances may be different from those who actually do not suffer from sleep disturbances. These considerations aside, Carskadon and Dement report that 16 males (88%) and 16 females (72%) demonstrated at least one sleep apnea episode, while 8 males (44%) and 7 females (31.8%) have high levels of sleep apnea (AI>5). Males with apnea showed a mean number of 51, while females showed a mean number of 34. Sex differences appear to have fallen out at this age, while the restricted range of this extreme age sample does not lend itself to a correlational analysis of age versus apnea. In another study of limited generalizability, Kreiss et al. (1982) randomly selected inpatients on a Veterans Administration medical ward. These patients, all presumably male, numbered 26. Further data reported were

sketchy, but 7 (27%) met the sleep apnea syndrome criterion of >30 episodes of sleep apnea. The fact that these subjects were patients on a medical ward obviously restricts generalizability of these findings. Finally, in the only truly random sampling reported, Ancoli-Israel et al. (1982) present initial data on randomly selected subjects. Forty subjects (sex not reported) with a mean age of 71.5 were studied. Thirteen (32.5%) met the sleep apnea syndrome criterion of 30 or more apneas. The sleep apnea subgroup was older, 74.2, than the full sample.

The data collected from relatively random sampling are primarily based on aging populations (>60). The data from these studies suggest that between 32.5% (Ancoli-Israel et al., 1981) and 37% (Carskadon and Dement, 1981b) of aging subjects suffer high levels of sleep apnea (AI>5). An even larger percentage, perhaps greater than 75%, suffer at least some episodes of sleep apnea. A major deficiency in these randomly sampled studies is a lack of data on younger subjects.

Thus data collected under different sampling procedures yield variable incidence rates of sleep apnea and AI>5. Subjects without sleep or respiratory complaints have a very low incidence (perhaps 0) of AI>5, between 14% and 45% of males surveyed had at least some apnea, while females ranged between 10% and 40% experiencing some apnea. Sampling subjects with sleep or respiratory complaints suggested that subjects suffering respiratory

difficulties had very high incidences of apnea (almost 100% for both males and females) with increase of incidence of AI>5 (55% for males, 23% for females). Sampling without regard to sleep or respiratory difficulties is largely confined to aging populations. Incidences of apnea in these aging populations would seem to be rather high (88% males, 72% females) while incidence of AI>5 seem to be in the range of 32%-37%.

It is clear that different populations (as defined by sampling strategies) suffer different incidences of sleep apneas and AI>5. The clinician dealing with sleep disorders would be wise to consider the acturial base rates of apnea and AI>5 provided by these data. It is apparent that sex, age, and respiratory status are significantly related to the incidence rates of SAA and SAS. These factors must be considered in any study of apnea and associated deficits.

Temporal Characteristics of Apneas

The temporal characteristics of sleep apneas represent a potentially important variable. Above it was shown that a wide variability in number of sleep apneas occurs, and the arbitrary nature of the division between SAA and SAS subjects was noted. Therefore, it is of interest to determine whether the duration of sleep apneas provides a more reliable distinction between the two groups. Another variable of interest involves the placement of apneas within sleep, as Guilleminault et al. (1976) noted that

normals might experience apneas during REM without pathological consequence. Therefore, data available on these two issues will be reviewed, including only studies with a sample size great than 10 (with one exception).

Reports on normal subjects below 30 years of age are somewhat rare, although some do exist. Bixler et al. (1982) included a group aged 18-29 years (M = 13, F = 17). One subject in this group had sleep apneas (12) with a mean duration of 15 seconds. Bixler et al. noted that most apneas occurred in Stages 1 and REM sleep. Part of the sample of Block et al. (1979), the females, had a mean age of 29. Three of these subjects showed apneas with a mean duration of 14 seconds. Again, a disproportionate number of apneas occurred in Stages 1 and REM. Thus in normal subjects under 30, apneas are somewhat rare, with a mean duration of approximately 15 seconds when they do occur. Most apneas occur in light and REM sleep.

More data are available on normal subjects between 30 and 60. Guilleminault et al. (1978) do not report on duration of apneas in their sample aged 40-60, but they note that apneas occurred only in Stages 1 and REM. Bixler et al. (1982) reported that, in their 30-44 year old group, 5 subjects experienced sleep apnea with a mean duration of 13.1 seconds. A disproportionate number of apneas occurred in Stages 1 and REM. Block et al. (1979) studied 30 males with a mean age of 38, with 12 experiencing sleep apneas. These apneas had a mean

duration of 20 seconds and occurred most frequently (30/60) in Stages 1 and REM. Eight of 20 aging females, in the report by Block et al. (1980), had sleep apneas with a mean duration of 19 seconds. Sixty-two percent of apnea episodes occurred in Stages 1, 2 or REM. Thus in middle aged normal subjects, incidence of sleep apnea appears to rise, with a mean duration of between 13 and 20 seconds, perhaps slightly longer than in younger groups. Again, apneas occurred mostly in light (Stages 1 and 2) and REM sleep.

Duration data on aging normals are limited. Carskadon and Dement's (1981b) study of aging normals (M = 72, F = 74) does not report duration of apnea events. Similary, Ancoli-Israel et al. (1982) do not provide this information on their aged normals ($\bar{x}$ = 71.5). Bixler et al. (1982) noted a high incidence of apneas in their subjects over 60, but failed to report a mean duration for this group. Given the sketchy details reported for this group, it is difficult to draw any conclusions about changes in temporal duration or placement of apneas in aging normals.

To summarize the temporal data in normals, apneas appear somewhat rarely in normals below 30, with a mean duration of 15 seconds. Incidence of apneas increase between 30 and 60, with a wider variation in mean durations reported (13-20 seconds). Apneas occur most frequently in light and REM sleep in normals of all ages.

Temporal data on subjects diagnosed with sleep apnea syndrome (>30 or AI>5) primarily include patients between the ages of 30 and 60. The reason for the lack of older SAS subjects is unclear, particularly in light of data reported above, demonstrating very high percentages of SAS in certain groups of aging subjects.

Garay et al. (1981) studied 13 sleep apnea syndrome subjects. They divided these 12 males and 1 female into two groups, based on their daytime resting CO_2 levels. Subjects who were eucapnic during the day had a mean apnea duration of 16 seconds, while those who were hypercapnic had a mean duration of 17 seconds. No data on distribution relative to sleep stages were reported. Guilleminault et al. (1978) studied 50 predominantly male ($\bar{x}$ age 48) sleep apnea syndrome patients. Apneas in this population averaged 22 seconds in duration. Apneas were longest in REM, and few occurred in Stages 3 or 4 sleep. Fujita et al. (1981) studied 12 male SAS patients with a mean age of 43. Apnea episodes averaged 23 seconds in duration. Weitzman et al. (1980) studied 10 SAS males whose age ranged from 38-57. The mean duration of apneas in this group was 30 seconds. All apneas occurred in light or REM sleep. Orr et al. (1979) studied 4 hypersomnolent males diagnosed with SAS. A control group of 4 nonhypersomnolent subjects was matched on number of obstructions per minute. Mean age was 57 for asymptomatic and 42 for symptomatic subjects. Asymptomatic subjects

had apneas with a mean duration of 25.9 seconds, while symptomatic subjects had a mean duration of 20.8 seconds.

Several characteristics emerge from the group of reports on SAS subjects. There is wide variability in duration of apneas, with reported means ranging from 16-30 seconds. The data available on placement of apneas in sleep suggest that in SAS subjects most apneas occur in light and REM sleep.

Comparison of data on normal and SAS subjects reveals substantial overlap between mean duration of apneas in SAS subjects (13-20 seconds) and SAS subjects (16-30 seconds). Particularly interesting was the Orr et al. (1979) study which demonstrated a lower mean duration of apneas for hypersomnolent subjects than for nonhypersomnolent subjects. Data on temporal placement of apneas show most events occurring in light or REM sleep for both normal and SAS subjects. Taken together, these data suggest that substantial overlap exists on temporal variables between normal and SAS subjects indicating a limited utility for diagnostic purposes.

Variables Associated With Sleep Apnea Syndrome and Activity

It was noted above that several variables have been suggested as associated with increased incidences of sleep apneas and SAS. These variables represent potential "markers" of subpopulations which might experience higher incidences of sleep apnea activity. These primary

associated variables include sex, age, snoring and obesity. The data available on these variables and their relationships to sleep apnea activity will be reviewed, followed by a brief discussion of their relevance to experimental methodology.

Regarding sex variables, as previously noted, Guilleminault et al. (1978) found 96% of their SAS patients to be males. In the Block et al. (1979) study of nonsleep disturbed subjects, 40% of the males in the sample had at least one episode of apnea, while only 15% of the females so suffered. Bixler et al. (1982) noted a trend toward more sleep apnea activity in males. Block et al. (1980) studied 20 post menapausal females and found apnea activity in 40% of them, leading them to suggest that some factor associated with menapause (e.g., progesterone) might somehow "protect" premenapausal females from apneas, and that this factor along with its benign influence was lost with menapause. This explanation predicted the low level of apnea activity in younger females, as well as the heightened apnea activity of aging females. While the data of Carsakdon and Dement (1981b) show aged females to be close to aged males in percentage exhibiting sleep apnea activity, a report by Smallwood et al. (1983) found no evidence of sleep apnea activity in their 6 elderly (post menapausal) females, while elderly males showed significant levels of apnea activity. The limitations of the sample size in the Smallwood et al.

report might explain this discrepancy as representing a sampling bias. Taken together, this evidence strongly supports the notion that in young and middle aged populations, sleep apnea is a male phenomenon. Additionally, evidence points toward a closing of the gap between females and age matched males as the former group passes menapause.

A second factor which has been implicated in sleep apnea activity is age. Webb (1974) found that his subjects exhibiting sleep apnea activity were significantly older than his full sample. This was also the case for the subjects of Kales et al. (1982) and Ancoli-Israel et al. (1982). Smallwood et al. (1983) found that sleep apnea was an age dependent phenomenon with male subjects over 50 exhibiting significantly more apneas than those under 30. Other evidence includes that of Bixler et al. (1982) who found a positive correlation between age and apnea in their full sample, as did Block et al. (1980) in their post menapausal females. It seems clear from these data then that increasing age is a factor predisposing for sleep apnea activity.

Snoring has been closely associated with sleep apnea (Lugaresi et al., 1982). This may be due to a causal relationship or a single common pathway. Lugaresi et al. propose the latter explanation. Specifically, they suggest that both snoring and SAS are due to a sleep induced stenosis of the upper airway. With this premise

in mind, they conducted a survey of 1000 subjects on the incidence of snoring. Chronic snorers included 31% of the males and 19% of the females. In an elaboration of this study, Lugaresi et al. (1980) questioned 5713 individuals. In this sample, 24% of the males and 13% of the females were chronic snorers. Snoring increased with age, and by 60 years of age 60% of the males and 40% of the females snored. Of note was the observation that hypertension occurred more frequently in snorers than nonsnorers, suggesting that the former was more at risk for cardiovascular complications.

Virtually every study of SAS patients notes the presence of snoring in all these subjects (Sullivan and Issa, 1980; Block, 1980; Coverdale et al., 1980). This is true for both predominantly obstructive, and predominately central SAS subjects (Guilleminault et al., 1978). However, the presence of heavy snoring in asymptomatic (nonhypersomnolent) apneas is also well documented (Orr et al., 1979; Fisher et al., 1978; Berry and Block, 1983), as well as in otherwise normal subjects. These data may be taken as evidence for snoring as a necessary, but not sufficient, condition for the occurrence of sleep apnea.

The role of body weight in SAS is less clear. Recall that Pickwickian patients are invariably obese, as well as hypercapnic. Guilleminault et al. (1978) stress that SAS may occur in nonobese as well as obese subjects. However, Block (1980) states that he has found SAS

subjects to be uniformly obese. A review of the literature is in order to clarify this point. First normal, then obese, then SAS groups will be reviewed.

Bixler et al. (1982) found that their subgroup of subjects with sleep apnea activity weighed significantly more than the remainder of the sample. Kales et al. (1982) found that within their sample of 200 insomniacs and 100 normals, a significant positive correlation emerged between a weight:height ratio and apnea activity. Block et al. (1979) found a positive correlation between apneas, oxygen desaturation, and weight within their normal males, while females did not demonstrate this relationship. Using an older female sample, Block et al. (1980) found a positive correlation between weight and oxygen desaturation, but not apnea. Thus in normal subjects, there appears to be a positive relationship between weight and apnea activity, although this may be restricted to males.

A research approach which bears on this question involves studying obese subjects alone. Two studies on successive referrals for gastric bypass surgery were noted. Sicklesteel et al. (1981) found that of 19 successive referrals, all 14 males exhibited sleep apneas, while only 5 of the females showed evidence of oxygen desaturation alone. Harmon et al. (1981) studied gastric bypass patients and found 5 of 6 males to suffer apnea, as

opposed to none of the females. This evidence provides further evidence for a role of increasing weight in apnea.

The data on symptomatic SAS subjects are more complex. Several studies (Sullivan and Issa, 1980; Weitzman et al., 1980; Garay et al., 1981; Zwillich et al., 1982) report that all their SAS subjects were obese, although definitions of obesity either vary widely or remain unspecified. In contrast, Guilleminault et al. (1978) reported that only 60% of their SAS sample was greater than 15% above ideal weight. Coverdale et al. (1980) indicate that only two of their subjects proved to be obese, according to their definition (>125% of ideal weight). These reports suggest that most, although not all, SAS subjects are obese.

Several investigators have sought to compare weight in symptomatic (somnolent) and asymptomatic subjects with enough sleep apnea episodes to be diagnosed as SAS. Orr et al. (1979) compared 4 symptomatic SAS subjects with matched asymptomatic subjects. In this sample, symptomatic SAS subjects were heavier than asymptomatic subjects. Examination of the data of Berry and Block (1983) indicates that their symptomatic subjects were heavier than their asymptomatic subjects (118 kg vs. 91 kg). Standing in contrast to these data is a study reported by Fisher et al. (1978), which included 19 subjects referred for SAS evaluation. Based on number of apneas per night, Fisher et al. divided their subjects into 3 groups. Group

I had >100 apneas per night, Group II had >30 but <100 apneas per night, while Group III had less than 20 apneas per night. Thus Groups I and II were diagnosable as SAS (>30), while Group III was not. Obesity was present in Groups I and II, but in only 3 subjects in Group III. However, these differences were not statistically significant.

Taken together, this evidence suggests a positive relationship between weight and apnea in the general population. However, SAS patients are not invariably obese. Further, weight loss fails to result in a decrease in apneas in many SAS patients. Thus the relationship between obesity and full blown SAS is less than clear.

The preceding pages have investigated the currently understood role of several variables (sex, age, snoring and weight) in sleep apnea activity. Presently available data suggest that in young and middle aged subjects, apnea is a predominantly male phenomenon, although post menapausal females may close the gap. Increasing age is related to sleep apnea activity. Snoring, which occurs in a significant percentage of the general population, is thought to be a necessary but not sufficient condition for SAS. Weight was shown to have a positive relationship to sleep apnea activity in the general population, although its presence or role in SAS is equivocable.

These conclusions have important implications for experimental designs directed at understanding sleep apnea

activity and its correlates in a subclinical population. It is clear from the earlier review of apnea incidence that sampling from the general population would result in a relatively low population of individuals with sleep apnea, an inefficent approach from the perspective of the limited resources available for research. Thus selection variables must be considered with one eye on efficiency and the other on protecting the generalizability of results. Selection criteria should also aim toward elucidating the relative roles and possible interactions of these variables in sleep apnea. Therefore, selection variables should have as straight-forward a relationship as possible with sleep apnea, seeking to answer more questions than they raise.

With these caveats in mind, the variables available as selection criterion will be reviewed and conclusions drawn about their relative merits. The first variable considered, sex, has been relatively well investigated. It is clear that sleep apnea activity is primarily a male circumstance. Therefore, the selection of female subjects is contraindicated from the standpoint of efficiency. Age has been demonstrated to exhibit a positive relationship with sleep apnea, indicating selection of older subjects. Snoring is another variable with a close relationship to sleep apnea. The apparently common mechanism of snoring and sleep apnea (stenosis of the upper airway) indicates that possibly very few subjects without snoring

suffer sleep apneas. A significant proportion of snorers might be expected to suffer apneas, while few nonsnorers might have apnea. The last variable, weight, while having a positive correlation with apnea activity in the general population, is of uncertain pertinence to SAS. Additionally, changes in weight may occur without changes in apnea activity. Therefore, this variable has a less than explicit connection to apnea activity and violates the second principle adopted to consider these variables.

This review of available data suggests that sampling aging, snoring, males would generate a high proportion of sleep apnea activity. External validity for this idea is drawn from its similarity to the "typical" SAS patient described earlier. Extant data suggest that it may also prove useful to utilize weight measures as a covariate, in an attempt to control its apparent influence on apnea activity.

Deficits Associated With Sleep Apnea Syndrome

Sleep Apnea Syndrome is thought to result in several deficits. These include cardiopulmonary complications, hypersomnolence, hypoxia and intellectual changes. Some researchers have suggested that these deficits may be present, in an attenuated form, in subclinical apnea (Ancoli-Israel et al., 1981; Carskadon and Dement, 1981b). A discussion of the evidence for the presence of these deficits will be presented, followed by proposals for appropriate measures of these variables.

Cardicpulmonary Deficits

Cardiopulmonary complications have been reported as concomittants of SAS (Guilleminault et al., 1978). Coccagna et al. (1972) reported high incidences of hypertension and congestive heart failure in their SAS subjects. Schroeder et al. (1978) studied 22 SAS patients with a mean age of 47. Six subjects had waking systemic hypertension, and several had waking cardiac abnormalities. During sleep studies, 20 patients developed significant rises in systemic arterial pressure which cycled with episodes of apnea, while 21 patients developed pulmonary arterial hypertension. Tracheostomy reversed all these abnormalities, strongly implicating the apneas in their etiology. Tilkian et al. (1978) studied 25 male SAS subjects with a mean age of 44. Twenty-four of the 25 showed sleeping sinus arrhythmias, while 9 developed more serious symptoms such as asystole. Seventeen of these patients received tracheostomy, which abolished all of these abnormalities. Experimental occlusion of the tracheostomy during sleep in 6 of these patients resulted in a return of the cardiopulmonary symptoms. Zwillich et al. (1982) studied six consecutive male SAS patients. In all patients, bradycardia accompanied any apnea with significant desaturation. Additionally, a significant correlation was noted between degree of desaturation and severity of bradycardia. Bradycardia was abolished or attentuated during administration of O_2 enriched air.

Zwillich et al. proposed that bradycardia during apnea results from increased vagal tone mediated by carotid body chemoreceptors. Fujita et al. (1981) reported on 12 male SAS patients. All reportedly suffered cardiac arrhythmias during sleep. The body of data suggests that SAS patients frequently suffer from cardiac abnormalities such as hypertension, arrhythmias, and bradycardia.

A second body of data exists which indicates that SAS patients do not invariably have cardiopulmonary complications. Coverdale et al. (1980) studied 14 patients, of whom 8 were diagnosed with SAS. Only 2 of these patients had evidence of corpulmonale, while 2 more had systemic hypertension. None of these patients demonstrated severe brady or tachycardia during sleep. In Orr et al. (1979), 8 patients, all of whom were technically diagnosable as having SAS, all symptomatic (somnolent) patients had evidence of right sided heart failure as well as frequent arrhythmias during apneas. Asymptomatic subjects had none of these symptoms. Kreiss et al. (1982) studied 26 Veterans Administration ward patients and found 7 to have a SAS. The SAS patients had significantly more signs of congestive heart failure, but not hypertension or angina. Ancoli-Israel et al. (1981) sampled 24 elderly subjects with complaints of sleeping respiratory disorders. Nine of these subjects were diagnosable as SAS, but this group did not have significantly more heart

disease or hypertension. Thus a group of SAS patients without evidence of heart disease exists.

Taken together, these data indicate that cardiac complications frequently, but not inevitably, accompany a sleep apnea syndrome. That a large number of apneas may be present without a significant increase in cardiopulmonary complications is demonstrated by the Orr et al. and Ancoli-Israel et al. studies. As the relationship between these complications and a full blown SAS is unclear, the possibility of cardiopulmonary sequelae from a subclinical level of apneas is even more uncertain. However, an assessment of cardiopulmonary status is indicated by the frequent association of cardiopulmonary complications with sleep apnea syndrome.

Arousal Deficits (Hypersomnolence)

Excessive Daytime Sleepiness (EDS), or hypersomnolence, has been described as the single most common result of SAS (Dement et al., 1978). Indeed, patients who meet the criterion of number of apnea episodes and exhibit EDS are described as symptomatic, while those with number of apneas alone are labeled asymptomatic (Orr et al., 1979). As an aside, this distinction illustrates again a central issue of SAS. If patients exhibit the number of apneas qualifying them for SAS, but no other pathology, are they suffering from a pathological process? Dement et al. (1978) believe that they are. They suggest that most, if not all, patients with a clinically elevated number of

apneas actually suffer EDS, but that it is masked by two factors. Dement et al. noted that SAS patients may deny somnolence while literally falling asleep before the clinician. They speculate that this results from a response bias against acknowledging illness or a change in subjective frame of reference about just what alertness is. Thus EDS may be denied by patients for reasons which may be outside the clinician's control or knowledge. Alternatively, Block et al. (1979) propose that asymptomatic SAS patients are suffering a subclinical level of fallout from their frequent apneas. As years pass, increasing weight or cumulative effects of desaturation eventually lead to a full blown hypersomnolence--Sleep Apnea Syndrome. A final possibility is that nonhypersomnolent subjects with frequent apneas exhibit a completely benign process totally unrelated to that found in symptomatic SAS patients. It would seem that delineation of the level of EDS in subjects with subclinical levels of apnea may help clarify this issue. This notion will be elaborated below.

The somnolence deficit which is noted in full blown SAS patients is commonly reported. Dement et al. (1978) describe impairments in continuous performance of virtually any activity. Sleep Apnea Syndrome patients reportedly fall asleep at outdoor stadiums, in front of classes, and while treating patients. Excessive Daytime Somnolence is described in every SAS patient reported in

experimental protocols by Weitzman et al. (1980), Fujita et al. (1981), Zwillich et al. (1982), Garay et al. (1981) and Sullivan and Issa (1980). At the same time, subjects who are asymptomatic for EDS but with the necessary number of apneas to be diagnosed as SAS are described by Orr et al. (1979) and Smirne et al. (1980) as well as others. However, it should be noted that the latter studies relied on global reports of somnolence, rather than quantified data. Recalling the criticism of Dement et al. (1978) of this technique as vulnerable to subjective bias, these asymptomatic patients may have unreported or undetected somnolence.

Excessive Daytime Somnolence appears to be frequently concomittant with Sleep Apnea Syndrome. Thus its possible occurrence in subclinical populations seems worthy of investigation.

Oxygen Desaturation and Cognitive Deficits

One deficit which appears in SAS patients is oxygen desaturation which accompanies apneas. When apnea begins, arterial oxygen saturation begins to fall, and may continue falling throughout the event. An early technique utilized in studying oxygen saturation levels involved periodic blood samples drawn from arterial sources. Birchfield et al. (1958) studied 11 normal males with a mean age of 23. Daytime oxygen saturation in these subjects averaged 96.5%. These values fell during sleep to 95.3%. Later, Orr et al. (1979) studied 8 males who had

been matched on number of apnea events. Asymptomatic (nonhypersomnolent) subjects fell from a baseline O_2 saturation of 80 mm (Hg) to a mean maximum desaturation of 54 mm (Hg) during sleep. Symptomatic subjects fell from a baseline of 54 mm (Hg) to a mean maximum desaturation of 35 mm (Hg) while asleep. Orr et al. suggested that the more severe desaturation which accompanied apneas in symptomatic subjects underlaid their somnolence and other complications. However, these conclusions are vulnerable to certain methodological criticisms, as Block (1980) points out. Specifically, periodic sampling may well fail to detect the multiple brief desaturations associated with SAS, rendering this technique potentially insensitive to important events.

In an attempt to provide more representative data on desaturation, Block et al. (1979) utilized an ear oximeter in studying saturation in normal subjects. An ear oximeter provided a continuous, accurate readout of moment to moment arterial oxygen levels. Thirty males (mean age 38) and 19 females (mean age 27) were studied. Of the 30 males, seventeen suffered at least one episode of desaturation, falling from a mean saturation of 95% to a maximum desaturation of 84% during sleep. In contrast, no episodes of desaturation were noted in the sample of premenapausal females (baseline O_2 saturation: 96%). The oxygen desaturations of the males were always found in association with breathing abnormalities or snoring. A study

of oxygen saturation in 20 post menapausal females was reported by Block et al. (1980). Eleven of these women exhibited desaturation with several subjects desaturating to less than 85%. Dolly and Block (1982) studied a group of 17 males and 3 females with a mean age of 49 years. These normal subjects dropped from a mean baseline saturation of 96.3% to a mean maximum desaturation of 88.3%. This evidence indicates that desaturations of 10-12% are common in normal males and post menapausal females while premenapausal females rarely, if ever, desaturate.

Oxygen saturation levels in SAS patients are not commonly reported. Using an ear oximeter, Garay et al. (1981) studied 11 SAS patients who were divided into 6 daytime eucapnics and 7 daytime hypercapnics. Eucapnics fell from a baseline saturation of 95% to a mean maximum desaturation of 73.5%, while hypercapnics fell from a baseline saturation of 89% to a maximum desaturation of 62.8% (calculated from tabled data). These data were collected during daytime "nap" studies, however, and hence is somewhat questionable. Berry and Block (1983) recorded 9 heavy snoring males who suffered many apneac events. Four subjects were somnolent, while 5 were not. Symptomatic subjects fell from a baseline of 95% to a mean maximum desaturation of 44%, while asymptomatic subjects desaturated from a baseline of 94% to a mean maximum desaturation of 85%.

Data on desaturation are interesting from several perspectives. First of all, Sleep Apnea Syndrome subjects seem to desaturate more heavily than normals, with Berry and Block's symptomatic group desaturating up to 50% and the subjects of Garay et al. desaturating about 22%, compared with normal desaturation levels of 10-12%. Secondly, amount of desaturation distinguished symptomatic (hypersomnolent) from asymptomatic subjects in the data of both Orr et al. and Berry and Block. Additionally, two points relevant to methodology emerge. Measures of oxygen desaturation seem crucial to understanding sleep apnea and its effects, and ear oximetry appears to provide a proven, valid measure of this variable.

Weitzman (1979) has suggested that the pathological process in SAS is the hypoxia of desaturation in apneac episodes. While cognitive and intellectual changes in SAS have been only anecdotally reported (Guilleminault et al., 1978), hypoxia does seem a plausible potential cause of these changes. Thus oxygen desaturation appears to be a reliable consequence of sleep apnea syndrome, while cognitive/intellectual changes are putative sequelae.

In summary, a review of deficits found in sleep apnea syndrome subjects suggests that cardiopulmonary complications, excessive daytime sleepiness, oxygen desaturation and cognitive/intellectual changes are frequently associated with this syndrome. An assessment of these variables in a subclinical population seems indicated by

these data. Below a discussion of measurement issues and proposal assessment of these variables appears.

Measurement of Deficits Found in Sleep Apnea Syndrome

Above it was noted that cardiopulmonary complications, excessive daytime sleepiness, nocturnal oxygen desaturation and cognitive/intellectual changes are common deficits of sleep apnea syndrome. A discussion of measurement issues and proposed measurement devices for these variables will be presented below.

Measurement of Cardiopulmonary and Health Deficits

Cardiopulmonary deficits are thought to be frequent sequelae of sleep apnea syndrome. Thus an assessment of blood pressure as well as self reports of hypertension and heart trouble seems indicated in subclinical apnea subjects. Additionally, a general survey of health status, such as that provided by the Cornell Medical Index (CMI; Broadman et al., 1949) would also screen for other health deficits. The CMI provides an overall score indicating number of symptoms endorsed, as well as subscales on several symptom categories. Separate examination of subscales on respiratory, cardiopulmonary, and neurological subscales seems appropriate. Assessment of these variables provides a broad health screening, as well as a detailed analysis of symptoms found in sleep apnea syndrome.

Measurement of Arousal Deficits (Hypersomnolence)

Excessive daytime sleepiness is a common sequela of sleep apnea syndrome. Measurements of the sleep/wake cycle of subclinical apnea patients thus seems indicated. A sleep questionnaire assessing trait sleep habits seems in order, as well as 1 week sleep logs following the experimental night. The sleep questionnaire and sleep logs have been used in ongoing research in W.B. Webb's studies of aging and sleep and seem an adequate assessment of sleep patterns of subclinical apnea subjects. Additionally, electroencephalographic recordings of sleep during the experimental night seem in order using a standard recording and scoring system (Agnaw and Webb, 1972). The assessment of daytime sleepiness is relatively new, only recently being the subject of investigation. William Dement and associates began to develop methods of quantifying somnolence in the early 1970s. The first attempt produced a subjective rating scale, the Stanford Sleepiness Scale (SSS; Hoddes et al., 1973). The SSS was a 7 point Likert scale with endpoints anchored on 1) feel active and vital; and 7) almost in reverie, sleep onset soon; with 5 points with statements reflecting various degress of somnolence in between. Patients rated their introspective level of sleepiness on this scale. Unfortunately, the SSS proved to be vulnerable to exactly the same difficulties as a global rating scale used on SAS

patients, i.e., response bias and altered frame of reference (Dement et al., 1978).

It was clear then that an objective measure of daytime somnolence was needed. With this goal in mind, Carskadon and Dement (1977) introduced the Multiple Sleep Latency Test (MSLT). This technique involved measuring the objective sleep latency during multiple nap attempts throughout the day. In a typical paradigm, a subject would be wired to an EEG and attempt to fall asleep at 2 hour intervals through the day. The latency to sleep in each nap was measured by determining the latency to the first epoch of Stage 1 sleep. In order to prevent significant amounts of sleep accumulating during testing, subjects were awakened after an epoch of sleep was observed. If no sleep was noted, subjects were disconnected after 20 minutes and allowed to resume other activities. Carskadon and Dement believe that this measures underlying physiological sleep tendency. This underlying tendency is thought to be modulated by alerting stimuli in the environment (Carskadon and Dement, 1982a). The validity of the test was established on normal subjects, who exhibited a biphasic curve of sleep tencency throughout a 24 hour period. Extension of sleep over typical lengths in normals (who are thought to be moderately chronically sleep deprived) saw a significant rise in average sleep latencies on the MSLT (Carskadon and Dement, 1979b), while chronic sleep restriction (5 hrs sleep per night) caused

significant declines in average sleep latencies (Carskadon and Dement, 1981a). Finally, total sleep deprivation led to a drastic decline in MSLT values, with averages plummeting below one minute (Carskadon and Dement, 1979a). Mean MSLT values showed recovery to baseline values after a full night's sleep for partially (5 hrs) deprived subjects, and recovery after two nights of ad lib sleep for totally sleep deprived subjects (Carskadon and Dement, 1979; 1981a). This body of evidence suggests that the MSLT is a reliable and valid index of sleepiness in normal subjects.

With its internal validity established, the MSLT was applied to somnolent populations. Dement et al. (1978) as well as Richardson et al. (1978) demonstrated that SAS and narcoleptic patients have significantly shorter latencies to sleep on the MSLT than normal subjects do. Hartse et al. (1979) found SAS subjects to have an average latency to Stage 1 of 2.5 minutes, while narcoleptics had a mean of 3.2 minutes. Both these latencies were significantly lower than those of a miscellaneous control group whose latencies were about 11.2 minutes. Hartse et al. (1980) found latencies to Stage 1 sleep as follows for various patient groups: Normals 12.2 m, Insomniacs 16.2 m, SAS 2.5 m, and Narcoleptics 3.2 m. The SAS and narcoleptic patients had significantly shorter latencies to Stage 1 sleep than insomniacs or normals. Roth et al. (1980) compared 10 SAS patients with 10 age matched controls.

The normals averaged 20.4 m to Stage 1 sleep while the SAS patients averaged 1.9 m. Zorrick et al. (1982) found mean MSLT latencies to Stage 1 sleep of 3.1 m for SAS subjects and 2.9 m for narcoleptics, significantly shorter than for patients with psychiatric disorders.

The chief difficulty remaining in judging the MSLT "reliable and valid" is external validation demonstrating that exceeding a certain mean latency is correlated with other deficits of performance. In some ways, low latencies on the MSLT may suffer the same limitations as sleep deprivation protocols; that is, demonstrating serious deficits is surprisingly difficult. At the same time, few would deny the subjective unpleasantness of sleep deprivation, which may be applicable to low MSLT scores. Thus the MSLT appears indicated in assessing excessive daytime sleepiness while the Stanford Sleepiness Scale (SSS) provides an index of the subjective experience of the subject. Application of both these measures to a subclinical apnea population would seem to adequately assess daytime sleepiness in these subjects.

Measurement of Hypoxia and Its Sequelae

Noctural desaturation is frequently noted in SAS patients. Therefore, it seems in order to examine the known sequelae of hypoxia of other etiologies in an attempt to determine variables or behaviors likely to be sensitive to the hypoxia found in SAS and SAA. Research on hypoxia varies systematically along two dimensions,

human vs. animal subjects and acute vs. chronic hypoxia. First, the data available on animals will be reviewed, followed by that extant on human subjects. Finally, behavioral variables sensitive to changes in these variables will be summarized.

The effects of chronic hypoxia on animals have not been exhaustively studied (Davis, 1975). One project which did examine this variable involved exposure of rats to up to 36 hours of 10% oxygen. Davis (1975) observed the behavior of these animals and concluded that they appeared normal. Although hyperventilation was noted, no permanent effects of the hypoxia were found. Hanbauer et al. (1981) examined the effects of 10% O_2 on rats exposed for up to 4 weeks. They found that relatively short term (2 days) hypoxia resulted in an increase in dopamine (DA) content in the carotid body. An increase in norepinephrine (NE) content was noted after 1 week of exposure. As the carotid bodies are implicated in the control of respiration, the authors concluded that different mechanisms are operative in the adaptation to short and long term hypoxia. Unfortunately, little other data have been reported on the chronic effects of hypoxia on more complex functioning. This is particularly problematic as it are these functions which are thought to be affected in humans exposed to hypoxia.

Certain aspects of acute hypoxia in rats have been carefully examined. Gibson et al. (1981) reviewed the

evidence which has been collected on neurotransmitter alterations in hypoxia. In brief, mild to moderate hypoxia, cerebral levels of ATP are normal, implying that energy supplies of neurons are not disturbed. In contrast, the turnover of certain neurotransmitters is altered. Gibson et al. note that oxygen is an important substrate for the synthesis of several neurotransmitters. When rats are exposed to acute hypoxia, synthesis of dopamine and serotonin is decreased, while absolute levels of tryosine, tryptophan, catecholamines, and serotonin remain constant. Continuing hypoxia leads to an adaptation resulting in normal turnover of these neurotransmitters. Gibson and Blass (1976) examined the affect of acute hypoxia on central acetylcholine (ACh). As in dopamine (DA) and serotonin (5-HT), acute hypoxia results in a decrease in synthesis in ACh, but not in the absolute level of ACh. Thus there is a substantial body of evidence indicating changes in central neurotransmitter levels in hypoxia. Generalizing from the animal data to human subjects, Gibson and Duffy (1981) suggest that these changes underlie the behavioral deficits of hypoxia in humans (which will be reviewed below).

Other variables have been examined in acute hypoxia in animals. Annau (1972) found that rats exposed to brief hypoxia exhibited decreased appetite, thirst, and self stimulation rates. Annau observed that brief hypoxia depressed all behavioral variables. Gellhorn (1951) found

that brief hypoxia of 4-7.5% O_2 abolished cortical responses to auditory stimulation. Sara (1974) trained rats in active one way avoidance tasks. Immediately after training, subjects were exposed to 3.5-4.0% oxygen. Rats tested at 1 and 3 hours post hypoxia avoided correctly, while those tested at 6 and 24 hours did not, leading Sara to suggest that hypoxia resulted in a memory retrieval deficit. Freides and Allweise (1978) also trained rats in one way avoidance and exposed them to 2.0% hypoxia immediately following training. These animals avoided at 12 and 200 minutes post hypoxia, but not at 90 minutes. Friedes and Allweise suggested that a sensitive period for hypoxia effects on training existed for 15 minutes after learning. Tauber and Allweise (1975) followed the same training/hypoxia paradigm and found avoidance impaired at 2.5 but not 4.5 hours. They suggest that hypoxia interferes with a medium term memory. While some of these data are conflicting, it appears that acute hypoxia depresses certain behavioral variables and interferes with aspects of memory processes.

While caution is in order when generalizing from animals to humans, several seemingly relevant points emerge from the review. Behaviorally, simple activities may be spared, although some depression of appetitive activities may occur, while more complex behavior dependent on memory processes may be altered. Of particular interest are the demonstrated alterations in

neurotransmitter turnover seen in hypoxia. It has been suggested that these subtle alterations may underlie the changes in complex behavior seen in hypoxic humans.

Data on human performance after hypoxia have necessarily been reliant on fortuitous or weak manipulations. Although this may limit the usefulness of these data, it is at the very least highly suggestive of variables sensitive to hypoxia. Van Liere and Stickney (1963) note that acute hypoxia leads to confusion, headache, drowsiness, weakness and incoordination. After effects include headache, nausea and emotional lability. Richardson et al. (1959) found that acute, fatal hypoxia from surgery results in damage to cortical neurons, particularly in layers III and IV. Susceptible subcortical neurons include those of the corpus striatum and cerebellum. Plum et al. (1962) describe a syndrome of delayed postanoxic encephalopathy. After the acute coma resolves in 4-5 days, a brief period of normal functioning returns. Increasing irritability and confusion then emerge, with loss of coordination and memory, and diminished attention span. Typically, the lesion spares grey matter while affecting white matter. Devereaux and Partnow (1975) describe a patient who recovered from a delayed acute encephalopathy. Although IQ was relatively spared, severe dysarthria emerged. Relevant points which emerge from studies of acute hypoxia in humans suggest that sublethal

levels of hypoxia affect coordination, memory, attention span, and may result in headache, drowsiness, and nausea.

The effects of milder, chronic hypoxia are summarized by Gibson et al. (1981). At the oxygen pressure equivalent of 5,000 feet, impaired dark adaptation is noted. At 10,000 feet decreased concentration, hyperventilation, and short term memory deficits are noted. By 15,000 feet, euphoria and loss of both coordination and critical judgement are observed. Christenson et al. (1977) found significantly less visual signals detected at 17% O_2 than at 21%, suggesting reduced vigilance. McFarland (1937) studied men in ascents to high altitudes and concluded that subjects with slower rates of ascent performed better on unspecified psychological tests. West (1984) reports data collected on an expedition to Mt. Everest. Results of a neuropsychological battery indicated deficits in finger tapping, verbal fluency, verbal learning, short term memory, and expressive language. Thus the general affects of chronic mild hypoxia are thought to be deficits in dark adaptation, short term memory, critical judgement, motor coordination, verbal fluency, and vigilance.

One group of chronically hypoxia patients, those with chronic obstructive lung disease (COLD), has been relatively well studied with sensitive neuropsychological instruments and is deserving of a more painstaking review. Krop et al. (1973) studied COLD patients before and after they received oxygen supplements. The WAIS,

Wechsler Memory Scale (WMS), Bender-Gestalt, Bender Gestalt Interference Procedure, Facial Recognition and Finger Tapping tests were administered to COLD and control subjects. Subjects receiving supplementation improved significantly more than controls on WAIS Full Scale IQ, Performance IQ, Wechsler Memory Quotient, both Bender procedures and Finger Tapping. Grant et al. (1982) studied another group of COLD patients. They administered the Halstead-Reitan Battery, Aphasia Screening Test, Trailmaking Test, Russell modification of the Wechsler Memory Scale, Tactile Memory test, and the WAIS. In COLD subjects, deficits were found relative to controls on all variables except Reitan Rhythm, Aphasia Screening and WMS Logical stories. Grant et al. concluded that COLD patients exhibited deficits on a global impairment rating, attention, abstracting ability, complex perceptual motor tasks, simple sensory and motor tasks, and memory tasks. Low but significant negative correlations were reported between several measures of oxygen saturation and both Halstead Impairment Index and Global Impairment Rating. Grant et al. speculated that floor effects resulted in low variability in P_AO_2 levels among COLD patients and kept these correlations low. They further suggested that the neuropsychological deficits observed in these patients resulted from the oxygen want found in these subjects.

Thus data available on humans indicate that dark vision, memory, motor coordination, critical judgement,

verbal fluency, and signal detection are affected by acute hypoxia. Animal data suggest that sensitivity of memory processes to hypoxia, while data from chronic hypoxia humans indicate that attention, vigilance, abstracting ability, complex perceptual motor skills, as well as motor and sensory abilities are also impaired by hypoxia. While none of these findings are unequivocally directly applicable to the brief, acute, desaturation occurring during apnea, they are, at the very least, indicative of abilities sensitive to hypoxia in humans.

A neuropsychological battery sensitive to these abilities includes Wechsler Adult Intelligence Scale (WAIS; Wechsler, 1955); Wechsler Memory Scale (WMS; Wechsler, 1945) including the Russell delayed memory aspects (Russell, 1975); Rey-Osterreith Complex Figure (Osterreith, 1944); Hooper Visual Organization Test (Hooper, 1958); Verbal Fluency Test (Halstead, 1947); Wisconsin Card Sort (Berg, 1948); and the Finger Tapping Test (Halstead, 1947). Administration of this test battery provides a broad screening of neuropsychological functioning, with a particular emphasis on those abilities known to be sensitive to hypoxia. Application of this battery to subclinical apnea subjects provides a sensitive indicator of possible hypoxic brain dysfunction.

In summary, alterations of sleep/wake cycles appear to be present in sleep apnea syndrome patients. Thus assessment of these variables in a subclinical population

is indicated. An adequate description of the sleep/wake cycle would seem to include sleep questionnaire, sleep log, overnight EEG, multiple sleep latency test, as well as several Stanford Sleepiness Scale ratings.

Statement of the Problem

Sleep Apnea Syndrome is a clinical entity with seemingly serious consequences. Although the nocturnal apneas found in this illness are thought to be the cause of the associated deficits, the identification of seemingly asymptomatic subjects with a number of apneas comparable to those found in SAS throws doubt onto this formulation. Despite this evidence, the recent discovery that apneas occur in significant numbers in the general population has led to speculation that this subclinical level of apnea may be the cause of various pathological processes. At present, there is little evidence to support or refute this notion.

The present report evaluates this issue through a detailed study of a group of subjects thought to be at risk for sleep apneas. Aging, heavy snoring males were recruited, and a comprehensive analysis of their respiratory, health, neuropsychological, and sleep/wake cycle status was carried out. Thus potential relationships between respiratory disturbances and variables known to be disrupted in sleep apnea syndrome patients could be evaluated. This approach also allowed exploration of the

possible risk factors associated with subclinical sleep apneas.

CHAPTER TWO
METHOD

Subjects

Heavy snoring males were recruited via newspaper advertisements, notices, and phone calls to a list of aging subjects reported by Webb (1982). Participants were required to be male, self reported heavy snorers, over 30 years of age, and in general good health (i.e., self described healthy and normal and not under the active care of a physician for illness). Subjects with a history of head trauma or alcoholism were excluded. Potential subjects who met these criteria were offered a chance to participate in a "snoring study" in which they would complete testing during an evening, sleep overnight in a lab with several physiological parameters recorded, and complete one week's worth of "sleep logs," for a payment of fifty dollars. Volunteers were scheduled on a first come, first served basis. A total of 60 subjects were studied, with 9 dropped because of technical problems with their overnight recordings and 5 excluded because of health problems. Thus 46 subjects represented the final sample. These 46 subjects had a mean age of 49.9 (sd 13.1) and represented a wide cross section of the population, ranging from the unemployed to university

professors. All subjects completed and signed an informed consent agreement.

Apparatus

During the evening testing, all subjects received a blood pressure check with a standard hospital cuff. The measurement was made from a seated position. Overnight recordings were made in a quiet, darkened room with the subject sleeping on a standard hospital bed. All nocturnal physiological recordings were routed through a Grass Polygraph (model 7D). Electrodes for electroencephalographic recordings were mounted in three pairs using sites F2/F8, PZ/T6, RE/LE from the international 10/20 system of placement. These electrodes were affixed to the scalp with collodion soaked gauze pads dried with an air hose. Respiratory measures included measurement of chest and abdomen wall movement derived from impedence measures monitored from surface electrodes (3M Ag/AgCl #2246) placed on the lower chest and just above the navel. The signal from these electrodes was passed through an impedence convertor and onto the polygraph. Oral and nasal airflow was recorded by thumistors (TCT-1R Transducer-Grass) clipped to the respective orifices. These signals were also routed through the polygraph. Electrocardiograms were monitored from modified bipolar chest leads (MCL_2). Finally, blood oxygen saturation was continuously monitored from a probe attached to the ear lobe, and analyzed by a Biox ear oximeter (Model 11A BTA

Co). All physiological variables were recorded on the polygraph's chart paper which was run at a speed of 10 mm/s.

Measures

Two classes of independent variables are identified, with the first being thumistor variables (those derived primarily from the nose and mouth thumistors). These included number of apneas and hypopneas, mean duration of apneas and hypopneas, mean low oxygen saturation in apneas and hypopneas, mean oxygen saturation change in apneas and hypopneas, and total seconds spent in apneas and hypopneas. Thumistor variables were separately scored by two trained raters, whose agreement appears in Table 2-1. An overall agreement of 85% was achieved. Disagreements were resolved by consensus scoring. The second class of independent variables included oxygen saturation variables (derived from a minute by minute rating of highest and lowest oxygen saturation from the overnight record). These variables included mean highest saturation, mean lowest saturation, and number of desaturations of 4 and 10% or more. In selecting these scoring criteria, several considerations were relevant. Initially, a system with reasonable interrater reliability was necessary. While published criteria for scoring apneas were not problematic, reliable scoring of hypopneas was not achieved until a desaturation criterion of 10% was introduced. In selecting measures of oxygen saturation, a mean high and

Table 2-1. Interrater agreement for respiratory events of 46 snoring males.

Consensus Scoring	Initial Agreements	Disagreements #1	Disagreements #2	Note
(178)	-	-	-	Scored by consensus
91	90	4	6	Consensus added 1
78	76	1	1	Consensus added 2
61	52	3	8	Consensus added 9
57	56	9	2	Consensus added 1
32	29	3	3	Consensus added 3
28	27	0	2	Consensus added 1
25	25	0	0	
19	16	4	0	Consensus added 3
17	17	0	0	
15	16	1	0	Consensus added 1
13	13	0	0	
7	7	0	0	
4	4	0	0	
4	4	0	0	
3	2	0	1	Consensus added 1
3	3	0	0	
3	0	7	2	Consensus added 3
3	3	0	0	
3	3	0	0	
1	1	0	0	
1	1	0	0	
1	1	0	0	
1	1	0	1	
1	0	0	1	Consensus added 1
1	1	0	0	
1	1	0	0	
1	1	0	0	
474(652)	450	37	36	

Note: 28 of the 46 subjects experienced at least 1 apnea or hypopnea.

low score seemed obvious. In order to assess the quantitative "impact" of numerous desaturations, a sum of 4% and 10% desaturation was tabulated. These selected parameters for thumistor and saturation variables allowed reliable scoring and a description of several aspects of nocturnal respiration.

Dependent measures fell into three broad classes: measures of sleep/wake status, measures of health status, and measures of neuropsychological status. Measures of the sleep/wake cycle included one week's sleep logs (derived variables included number of reports of daytime sleepiness, hours asleep, estimated sleep latency, number of wakenings after sleep onset, and minutes of waking after sleep onset), a sleep questionnaire (derived variables including hours of sleep usually obtained, number of naps, hours napping, quality of sleep, restfulness on awakening, depth of sleep, and amount of daytime sleepiness), the mean of the several Stanford Sleepiness Scale ratings, the two multiple sleep latency tests (derived variables included mean sleep latency and total minutes asleep in both naps) and the overnight EEG variables derived from the scoring system of Agnew and Webb (1972). Electroencephalographic variables included time in bed; pure sleep time; sleep efficiency index; number stage 0 periods; time % stage 0; sleep latency; time % stages 1, 2, 3, 4 and REM; latency first REM

period; mean REM period; mean REM cycle length; % slow wave sleep; and number of stage changes.

Measures of health status included height, weight, diastolic and systolic blood pressure, as well as the Cornell Medical Index. From the CMI, reports of hypertension and heart trouble were noted, as well as the total number of symptoms endorsed. Additionally, the scores for the scales tapping respiratory, cardiac, and neurological symptoms were tabulated separately.

Measures of neuropsychological status included the WAIS Verbal and Performance IQ's, the WMS Memory Quotient, delayed recall of the logical stories and the visual reproduction subtests of the WMS, delayed recall of the Rey complex figure, number of words generated in the verbal fluency test, number of correct sorts of the Wisconsin Card Sort, mean number of taps for the right and left handed finger tapping tests, and lastly the number of correct trials on the Hooper test.

These neuropsychological tests were chosen with two aims. First, an attempt was made to sample from each of several loosely bounded areas of cognitive skill. These included intelligence (both verbal and non-verbal), memory, both immediate and delayed (verbal and non-verbal), visuo-perceptual/organizational skills, language, and frontal self-regulatory skills. A second emphasis was on a relatively detailed analysis of areas previously shown to be sensitive to hypoxia. These sensitive areas

included memory, visuo-organizational skills, verbal fluency, and motor coordination. The chosen neuropsychological battery reflected these two aims. Thus the WAIS tapped intellectual functioning; the Wechsler Memory Scale with delayed recall of logical stories and visual reproductions as well as digit span and Rey Figure heavily sampled verbal and non-verbal memory; the Hooper tapped visuo-organizational skills; Verbal fluency sampled language skills; the Wisconsin card sort tapped frontal self-regulatory skill; and Finger tapping sampled motor functions. The chosen battery provided a broad screening as well as a detailed assessment of neuropsychological functions thought to be impaired by hypoxia.

Procedure

Subjects followed the schedule appearing below for the experimental night:

1800 Sign informed consent, blood pressure, height/weight, finger tapping, verbal fluency, subjective sleepiness (SSS-made every ½ hour till bedtime)

1830 Wiring for EEG

1900 Begin MSLT I (20 m)

1930 WAIS

2000 WMS, Hooper

2030 Graphesthesia, Luria motor programs

2100 Begin MSLT II (20 m)

2130 Rey figure, Wisconsin card sort

2200 Sleep Questionnaire, Cornell Medical Index, remaining testing

2230 Wiring for thumistor, EKG, respiratory effort, ear oximeter

2300 Lights out, begin recording

A night technician remained with the subjects throughout the night. Subjects usually awakened between 5 and 6 am, and later completed the one week's sleep logs.

Statistical Procedures

Several statistical procedures were utilized in evaluating the present data. One of the primary approaches was correlational, considered appropriate because of the exploratory nature of the study. Bearing in mind the possible alpha inflation of large correlational matrices, other approaches were also utilized to add confidence. Thus the sample was stratified by level of apnea/hypopnea, and oneway ANOVA procedures were used to evaluate between group differences. Additionally, nonparametric procedures were utilized where appropriate. Positive correlational results were considered against possible replication with other measures in the study, and in some cases multivariate procedures were added for further confidence. It is conceded that correlational approaches may carry the burden of possible spurious results, but it is believed that the various additional procedures outlineo above lend confidence to the findings.

CHAPTER THREE
RESULTS

Demographics and Incidence of Nocturnal Respiratory Disorder

Subjects were selected to fulfill several sampling requirements, including male sex, presence of heavy snoring, and self report of general good health. A total of 60 subjects were studied. Five subjects were later excluded when questioning revealed the presence of chronic alcoholism (2) and serious head trauma (3). Additionally 9 overnight records were rejected because of missing or unusable data. The characteristics of the final 46 subjects are detailed in Table 3-1. These snoring males had a mean age of approximately 50 years, a mean weight of approximately 190 pounds, and a mean educational level of 15 years of schooling.

Table 3-1. Demographic variables from 46 snoring males.

	M	SD	Range
Age	49.9	13.1	30-75
Weight (lbs)	189.3	34.9	125-250
Weight:Height Ratio (lbs:inches)	2.7	0.5	1.9-3.6
Education (years)	14.7	2.5	9-20

The respiratory records were annotated by two hour intervals following bedtime. From a total of 652 events scored, 150 (23%) occurred in the first two hours following bedtime, 185 (23%) occurred in the second two hours, 232 (36%) occurred in the third two hours, while 83 (12%) occurred in the final two hours. It should be noted that wakeup times varied considerably, making interpretation of the attenuated number of events in the final two hours somewhat problemmatic.

From a total of 578 events in which reliable sleep staging was achieved, 459 (78%) occurred in light slow-wave sleep (stages 1-2), while 118 (20%) began in REM sleep. Only 6 events (01%) occurred in slow wave sleep. These precentages must be considered in light of the relative distribution of sleep stages in these subjects: stages 1-2 (64%), stage REM (12%), stages 3-4 (10%), stage 0 (14%). This distribution suggests that the sleep time spent in stages, 1, 2, or REM must have provided the overwhelming preponderance of events in these stages. Sleep characteristics will be discussed in greater detail below.

As noted below, 28 of the 46 subjects experienced at least one episode of apnea or hypopnea. Table 3-2 presents the data on occurrence of at least one apnea/hypopnea, as well as the occurrence of a high level of apnea/hypopnea. Almost 2/3 of the sample had at least one apnea or hypopnea, while 13% had high levels of

Table 3-2. Incidence of low and high levels of apnea/hypopnea by age in 46 snoring males.

Age Group	N	Low Apnea/ Hypopnea	High Apnea/ Hypopnea
30-39	14	.71	0
40-49	7	.57	.29
50-59	11	.72	.27
60+	14	.43	.07
Overall	46	.62	.13

apnea/hypopnea. Note that subjects with high levels of apnea/hypopnea are included in the overall total of subjects with at least one event for the following analyses. The classification of "high" levels of apnea/hypopnea utilizes the criterion of an apnea + hypopnea index greater than 5, a frequently used clinical cut-off score. The table also presents the frequency of respiratory distress broken down by age. No simple age related trend is apparent, and a X^2 analysis of the two factors of age and respiratory distress was not significant for those with at least one event (X^2=3.2; p=NS), or for those with high levels of apnea/hypopnea (X^2=5.9; p=NS).

A further investigation of possible age by level of apnea activity involved division of the sample into those above and below 60 years of age crossed with those above and below 5 events/hour. The X^2 value for this comparison was also nonsignificant (X^2=0.6; p=NS). Subjects were

also divided into those above and below the mean weight: height ratio (2.7) and crossed with those with and without at least one event or high levels of apnea/hypopnea. Both these non-parametric tests were also non-significant (X^2=.01; p=NS; X^2=1.5; p=NS).

Table 3-3 utilizes Pearson correlations to explore possible relationships between demographic variables (age, weight, weight:height ratio) and nocturnal respiratory indices (apnea index, apnea + hypopnea index, seconds in events, mean high saturation, mean low saturation, number of desaturations ≥4%, and number of desaturations ≥10%). Again, age displays little relationship with respiratory indices, but substantial correlations between weight and various respiratory indices are apparent.

Table 3-3. Significant (p<.05) Pearson correlations between nocturnal respiratory variables and demographic variables in 46 snoring males.

Respiratory Variable	Age	Weight	Weight:Height Ratio
Number of Apneas			
Number of Apneas+Hypopneas			.265
Apnea Index			
Apnea+Hypopnea Index		.260	.306*
Mean High Saturation		-.323*	-.363*
Mean Low Saturation		-.397*	-.460*
Mean Saturation Change		.319*	.373*
Number of Desaturations ≥4	.287	.368*	.430*
Number of Desaturations ≥10			

*p<.01

In summary, non-parametric analyses failed to reveal significant relationships between age or weight and overnight respiration. However, Pearson correlations suggested that increasing weight is associated with deterioration of several noctural respiratory indices.

Because increasing apnea/hypopnea levels have been suggested to carry increasing risks for various deficits, the sample was stratified by level of apnea/hypopnea. The first group included those subjects without events (No events), those with at least one event but less than 5 events per hour (Low apnea/hypopnea), and those with 5 or more events per hour (High apnea/hypopnea). It should be noted that this division of subjects is slightly different from the earlier non-parametric analyses, because in this grouping low apnea/hypopnea and high apnea/hypopnea are mutually exclusive, while in the earlier analyses the group with at least one apnea/hypopnea included those with more than 5 events per hour.

Table 3-4 utilizes oneway ANOVA procedures to compare these groups on demographic and nocturnal respiratory variables. There were no significant between group differences on any of the demographic factors: age, weight, weight:height ratio, and education [$F(2,43)=2.1$, 0.6,0.8,0.7; p=NS]. Logically, both apnea and hypopnea indices were significantly different between groups [$F(2,43)=9.6$, $p<.0004$; 20.5, $p<.0000$]. Followup comparisons (Scheffe) indicated that the high

Table 3-4. Means and standard deviations for selected demographic and nocturnal respiratory variables in 46 snoring males grouped by level of apnea/hypopnea.

	No Apnea/ Hypopnea	Low Apnea/ Hypopnea	High Apnea/ Hypopnea
Age	52.3(12.7)	46.1 (13.5)	56.5 (9.3)
Weight (lbs)	185.6(34.8)	188.5 (37.6)	205.3 (24.3)
Weight:Height Ratio	2.7 (0.4)	2.7 (0.5)	2.9 (0.4)
Education (years)	15.2 (2.9)	14.6 (2.0)	13.8 (2.6)
Number of Apneas	0	5.0 (7.7)	24.5 (34.1)[a,b]
Number of Apneas+Hypopneas	0	7.3 (9.2)	81.7 (52.6)
Apnea Index	0	0.9 (1.1)	4.5 (5.9)[a,b]
Apnea+Hypopnea Index	0	1.4 (1.5)	19.5 (19.4)[a,b]
Seconds in Apneas/Hypopneas	0	129.4(167.1)	2325.5(1469.5)[a,b]
Mean Apnea Duration	-	13.4 (4.0)	17.8 (1.3)
Mean Hypopnea Duration	-	29.6 (21.2)	33.2 (14.5)
Mean High Saturation	95.5 (1.7)	95.3 (1.3)	94.9 (1.2)
Mean Low Saturation	94.3 (2.1)	93.1 (1.6)	89.0 (4.6)[a,b]
Number of Desaturations $\geq$4%	29.5(54.1)	58.2 (58.6)	143.2 (105.9)[a,b]
Number of Desaturations $\geq$10%	0.2 (0.7)	3.5 (6.3)	51.0 (48.7)[a,b]

[a] Significantly different from no sleep apnea/hypopnea.
[b] Significantly different from low sleep apnea/hypopnea.

apnea/hypopnea group was significantly different from the other two groups on these two indices. While mean duration of apneas and hypopneas was not significantly different between the high and low apnea groups [$F(1,25)=3.3$, 0.1; p=NS], total seconds in respiratory events was [$F(2,43)=50.4$, $p<.0000$], with followup comparisons showing that the high apnea/hypopnea group was significantly different from the other two groups. Turning to the oxygen saturation data, mean high saturation failed to reach significance [$F(2,43)=0.3$, p=NS]. However, mean low saturation, number of desaturations $\geq$4% and $\geq$10% were all significant [$F(2,43)=11.6$, $p<.0001$; 7.0, $p<.002$; 21.4, $p<.0000$], and followup comparisons showed that the group with high levels of apnea/hypopnea was significantly different from the other two groups.

Thus, division of the sample into levels of apnea/hypopnea resulted in groups which were not significantly different on demographic variables including age, weight, weight:height ratio, and education. However, the group with high levels of apnea/hypopnea had significantly more nocturnal events, time in events, and oxygen desaturation.

In summary, the present sample of 46 snoring males appears representative of those predisposed to experience sleep disordered breathing (middle-aged, snoring males). Sixty-two per cent of these subjects had at least one

apnea or hypopnea, while 13% had high levels of apnea/hypopnea. Most events occurred in light slow-wave or REM sleep. No effect of age on level of sleep disordered breathing was observed, although increasing weight was correlated with nocturnal respiratory events. When the sample was stratified by level of apnea/hypopnea activity, subjects with high levels of events had significantly more events and desaturations than the remaining subjects, although no significant differences were observed on age, weight or education.

Nocturnal Respiratory and Health Variables

Health variables including blood pressure readings and several scores derived from the Cornell Medical Index (overall number of symptoms endorsed, as well as number of symptoms endorsed from the respiratory, cardiopulmonary and neurological subscales) were evaluated initially through a matrix of Pearson correlations which included the respiratory variables (apnea index, apnea + hypopnea index, seconds in events, as well as mean high and low saturation and number of desaturations $\geq$4% and $\geq$10%). From a total of 42 correlations, three were significant at $p<.05$ or less: Systolic blood pressure and mean low saturation ($r=-.261$); Systolic blood pressure and number of desaturations $\geq$4% ($r=.373$); Overall number of symptoms endorsed on the CMI and mean high saturation ($r=-.254$). As a further exploration of possible relationships between blood pressure and apnea/hypopnea activity, subjects were

asked whether they had ever been diagnosed with hypertension. Thirty-three per cent of those with no events had diagnosed hypertension, as did 33% of those with low levels of apnea/hypopnea, while only 15% of those with high levels of apnea/hypopnea had diagnosed hypertension. These data do not support an increasing level of hypertension in subjects with high levels of apnea/hypopnea.

The subjects were grouped into the earlier delineated levels of apnea/hypopnea. Table 3-5 presents the means and standard deviations of health variables from the three groups. No dramatic trends are apparent in this table, and oneway ANOVA procedures confirmed this observation with no significant differences for: Diastolic BP, $F(2,43)=.01$, p=NS; Systolic BP, $F(2,43)=.1$, p=NS; CMI overall, $F(2,42)=.2$, p=NS: CMI respiratory, $F(2,42)=.5$, p=NS; CMI cardiopulmonary, $F(2,42)=.5$, p=NS; CMI neurological, $F(2,42)=2.2$, p=NS.

In summary, while correlational procedures suggesteo relationships between several oxygen saturation measures and blood pressure as well as overall number of symptoms endorsed on the CMI, oneway ANOVAs failed to reveal significant between group differences when subjects were stratified by level of nocturnal distress.

Table 3-5. Means and standard deviations for health related variables in 46 snoring males grouped by level of apnea/hypopnea.

	No Apnea/ Hypopnea	Low Apnea/ Hypopnea	High Apnea/ Hypopnea
Systolic BP[a]	129.1(14.2)	128.7(12.6)	127.0(7.5)
Diastolic BP	83.2(13.4)	83.9(11.0)	81.6(7.6)
CMI[b] Overall Score	14.7 (7.4)	16.1(10.5)	13.8(7.4)
CMI Respiratory Score	1.4 (1.2)	1.1 (1.8)	2.0(1.4)
CMI Cardiac Score	1.6 (1.3)	1.2 (1.2)	1.0(1.2)
CMI Neurological Score	1.2 (0.9)	1.6 (1.5)	0.8(0.8)

[a] BP = blood pressure.
[b] CMI = Cornell Medical Index.

Nocturnal Respiratory and Sleep/Wake Variables

EEG Data

Electroencephographic variables were recorded overnight for all subjects. Records were scored by a trained technician who utilized the system of Agnew and Webb (1972) to determine sleep stages. In three records, EEG tracings were judged inadequate for differential sleep staging. However, a judgement of sleep vs. wake was made for these subjects in order to form a basis for the respiratory indices. These three EEG records were excluded from the following analyses, leaving 43 records as a base for analysis.

Fifteen variables (time in bed, pure sleep time, sleep efficiency index, number of stage 0 periods, time % stage 0, sleep latency, time % stages 1, 2, 3, 4, and REM, latency 1st REM period, mean REM period length, mean REM

cycle length, % slow wave sleep), reflecting multiple aspects of the sleep of these subjects, were derived from the sleep stage scoring. Table 3-6 presents the means and standard deviations for these subjects. Although subjects spent over six hours in bed, the table indicates that not quite 5 hours were spent asleep. The remaining variables suggest that an increase in sleep latency, and time awake, is responsible for the diminished sleep time, while lighter sleep is also increased.

Table 3-6. Means and standard deviations of selected sleep variables from 43 snoring males.

	Mean	Standard Deviation
Time in Bed	377.3	45.1
Sleep Latency	29.2	32.9
Pure Sleep Time	288.7	75.8
Sleep Eificiency Index	.76	.16
Number Stage 0 Periods	8.6	5.6
Time % Stage 0	14.3	12.7
Time % Stage 1	3.3	2.8
Time % Stage 2	60.8	10.3
Time % Stage 3	3.4	2.4
Time % Stage 4	7.9	6.4
Time % Stage REM	11.5	7.2
Latency 1st REM Period	124.7	92.2
Mean REM Period Length	14.9	9.4
REM Cycle Length	74.9	57.7
% Slow Wave Sleep	12.9	8.3

Note: see text for explanation of N.

Partial correlations, controlling for age, were calculated between these sleep and the respiratory variables. Out of a total of 105 correlations, only one

was significant at $p<.05$ or less: Number of desaturations $\geq 4\%$ vs REM latency ($r=-.369$).

Table 3-7 presents the sleep variable means for the subjects grouped by level of apnea/hypopnea. The group with high apnea/hypopnea appears to spend more time awake, less time asleep, and achieve less slow wave sleep than the others. However, none of these differences proved significant. In fact, only one out of 15 oneway ANOVAs achieved significance: Time in bed, $F(2,40)=0.4$, p=NS; Sleep latency, $F(2,40)=1.7$, p=NS; Pure sleep time, $F(2,40)=0.3$, p=NS; Sleep efficiency index, $F(2,40)=0.2$, p=NS; Number of stage 0 periods, $F(2,40)=0.5$, p=NS; Time % stage 0, $F(2,40)=1.3$, p=NS; Time % stage 1, $F(2,40)=1.3$, p=NS; Time % stage 2, $F(2,40)=0.04$, p=NS; Time % stage 3, $F(2,40)=3.64$, $p<.04$; Time % stage 4, $F(2,40)=1.32$, p=NS; Time % stage REM, $F(2,40)=1.5$, p=NS: Latency 1st REM, $F(2,40)=0.8$, p=NS; Mean REM period length, $F(2,40)=0.3$, p=NS: Mean REM cycle length, $F(2,40)=0.9$, p=NS; % slow wave sleep, $F(2,40)=2.4$, p=NS. Scheffe followup procedures for time % stage 3 revealed no significant between group comparisons.

To summarize, EEG sleep measures indicatec lighter sleep then normal in this sample, with increases in awakenings and light slow wave sleep observed. Neither between group comparisons nor correlational procedures revealed significant interactions between sleep and nocturnal respiratory variables.

Table 3-7. Means and standard deviations of selected sleep variables from 43 snoring males grouped by level of apnea/hypopnea.

	No Apnea/ Hypopnea	Low Apnea/ Hypopnea	High Apnea/ Hypopnea
Time in Bed	376.1 (45.3)	382.2 (47.4)	361.2 (38.0)
Sleep Latency	20.2 (12.7)	38.5 (43.5)	20.4 (18.7)
Pure Sleep Time	292.7 (73.5)	290.9 (81.5)	265.4 (69.5)
Sleep Efficiency Index	.77 (.17)	.76 (.16)	.73 (.14)
Number Stage 0 Periods	9.5 (7.6)	7.7 (3.2)	9.2 (5.5)
Time % Stage 0	15.8 (12.9)	11.6 (12.4)	20.9 (12.6)
Time % Stage 1	4.1 (3.7)	2.6 (1.8)	3.5 (2.0)
Time % Stage 2	61.3 (8.0)	60.3 (12.9)	61.3 (1.3)
Time % Stage 3	2.8 (1.9)	4.3 (2.5)	1.5 (2.3)
Time % Stage 4	8.5 (7.2)	8.5 (5.6)	3.6 (5.1)
Time % Stage REM	9.7 (6.0)	13.3 (7.8)	9.1 (7.6)
Latency 1st REM Period	136.5(106)	107.5 (71.5)	156.4(125.4)
Mean REM Period Length	13.9 (8.8)	16.1 (9.8)	13.5 (11.1)
REM Cycle Length	80.0 (56.1)	78.7 (61.7)	41.6 (42.7)
% Slow Wave Sleep	12.8 (8.8)	14.6 (7.4)	5.9 (8.1)

Note: see text for explanation of N.

Daytime Sleepiness Data

Included among the measures of daytime sleepiness were the mean of the several Stanford Sleepiness Scale ratings, and two variables calculated from the two evening naps: mean sleep latency and total minutes asleep during the naps. These variables were correlated with the respiratory variables, resulting in a Pearson correlation matrix. From these 21 correlations, two emerged significant at $p<.05$ or less, both involving the mean Stanford Sleepiness Scale ratings. Mean SSS ratings were correlated with apnea index ($r=.297$), and apnea + hypopnea index ($r=.283$).

Table 3-8 presents the means and standard deviations for the subjects grouped by level of apnea/hypopnea. One-way ANOVA procedures were non-significant for all these variables [SSS: $F(2,38)=2.4$, p=NS; Mean sleep latency: $F(2,35)=0.4$, p=NS; Total minutes asleep: $F(2,35)=0.3$, p=NS].

Table 3-8. Means and standard deviations for daytime sleepiness variables in 46 snoring males grouped by level of apnea/hypopnea.

	No Apnea/ Hypopnea	Low Apnea/ Hypopnea	High Apnea/ Hypopnea
Stanford Sleepiness Scale	3.2 (.7)	3.6 (.8)	4.0 (.7)
Mean Nap Latency	14.5 (5.7)	15.5 (5.3)	13.4(3.4)
Total Minutes of Sleep in Naps	11.3(11.9)	9.6(10.8)	13.5(6.6)

In summary, correlational procedures suggested relationships between nocturnal respiratory variables and subjective sleepiness, while no reliable between group difference were noted on the nap or SSS variables.

Subjective Sleep Assessment

Two assessments of subjective sleep parameters were completed, including the sleep questionnaire and sleep log. Several variables were selected from the sleep questionnaire and included: usual hours of sleep, judgement of whether usual sleep was adequate, number of naps per week, hours napping per week, number of nightly wakenings, minutes of nightly wakenings, usual sleep latency, depth of sleep, and daytime sleepiness. These variables were correlated with the respiratory variables, for a Pearson matrix of 63 correlations. Table 3-9 presents the signficant correlations which emerged from this matrix. Several respiratory variables were associated with napping variables, while mean low saturation and number of desaturations $\geq$4% were associated with reported minutes of nightly wakenings.

Table 3-10 presents the means and standard deviations from the subjects grouped by level of apnea/hypopnea. Oneway ANOVA procedures revealed no significant between group differences on the selected sleep questionnaire variables [Usual hours sleep, $F(2,43)=0.6$, p=NS; Adequate sleep, $F(2,43)=0.3$, p=NS; Number of naps, $F(2,43)=2.9$, p=NS; Hours napping, $F(2,43)=0.8$, p=NS; Number of

Table 3-9. Significant ($p<.05$) Pearson correlations between nocturnal respiratory and sleep questionnaire variables in 46 snoring males.

	Number of Naps	Hours Napping	Minutes Nightly Awakening
Apnea Index			
Apnea+Hypopnea Index	.249		
Seconds in Events	.331		
Mean High Saturation			
Mean Low Saturation			.307
Number of Desaturations ≥4%	.283		-.291
Number of Desaturations ≥10%	.403	.378	

Table 3-10. Means and standard deviations of sleep questionnaire variables derived from 46 snoring males grouped by level of apnea/hypopnea.

	No Apnea/ Hypopnea	Low Apnea/ Hypopnea	High Apnea/ Hypopnea
Mean h. Sleep	7.4 (.9)	7.0(1.6)	7.5(1.0)
Adequate Amount?	1.9 (.4)	1.8 (.4)	2.0(0)
Number of Naps/Week	1.8(1.5)	2.3(2.6)	4.3(2.2)
Hours Napping/Week	2.6(1.8)	3.5(2.7)	4.0(2.7)
Number of Nightly Wakenings	1.1 (.9)	1.5(1.3)	1.8 (.4)
Minutes Nightly Wakenings	1.9(1.1)	1.5(1.0)	1.5 (.8)
Sleep Latency	2.0 (.9)	2.0 (.6)	2.0 (.6)
Depth of Sleep	2.4 (.8)	2.1 (.9)	3.0(0)
Daytime Sleepiness	1.6 (.6)	1.9 (.4)	1.8 (.4)

awakenings, $F(2,43)=0.9$, p=NS: Minutes of awakening, $F(2,43)=0.8$, p=NS; Sleep latency, $F(2,43)=0.01$, p=NS; Depth of sleep, $F(2,43)=2.6$, p=NS; Daytime sleepiness, $F(2,43)=1.8$, p=NS].

Means were calculated from the 7 day sleep logs, and the following variables were selected for analysis: reports of daytime sleepiness, number of naps, minutes napping, total bedtime, sleep latency, number of awakenings, minutes of awakenings. These variables were correlated with the respiratory indices to form a Pearson correlation matrix totalling 49 correlations. Table 3-11 presents the 6 significant ($p<.05$) correlations which emerged. Again, number of desaturations were associated with reports of napping, while mean high saturation was associated with total bedtime, sleep latency, and minutes awake, and mean low saturation was associated with minutes awake as well.

Table 3-12 presents the means and standard deviations for the subjects divided into levels of apnea/hypopnea. Oneway ANOVA procedures failed to reveal significant between group differences [Daytime sleepiness, $F(2,35)=0.6$, p=NS; Number of naps, $F(2,35)=0.3$, p=NS; Minutes of napping, $F(2,35)=1.3$, p=NS; Total bedtime, $F(2,35)=0.7$, p=NS; Sleep latency, $F(2.35)=0.2$, p=NS; Number of awakenings, $F(2,35)=0.2$, p=NS; Minutes of wakenings, $F(2,35)=.0001$, p=NS].

Table 3-11. Significant ($p<.05$) Pearson correlations between nocturnal respiratory and sleep log variables in 46 snoring males.

	Number of Naps	Total Bedtime	Sleep Latency	Minutes Nightly Wakenings
Apnea Index				
Apnea+Hypopnea Index				
Seconds in Events				
Mean High Saturation		.237	.250	.359
Mean Low Saturation				.265
Number of Desaturations ≥4%	.240			
Number of Desaturations ≥10%	.240			

Table 3-12. Means and standard deviations of sleep log variables derived from 46 snoring males grouped by level of apnea/hypopnea.

	No Apnea/ Hypopnea	Low Apnea/ Hypopnea	High Apnea/ Hypopnea
Daytime Sleepiness	1.9 (.9)	1.9(1.1)	2.4 (.3)
Number of Naps	0.2 (.2)	.3 (.4)	.3 (.3)
Minutes Napping	0.0(0)	.2 (.5)	0 (0)
Total Bed Time	6.5(3.1)	5.8(3.4)	7.5 (.7)
Sleep Latency	10.5(8.1)	11.1(9.8)	8.4(4.7)
Number of Wakenings	1.3(0.8)	1.3 (.9)	1.3 (.2)
Minutes Waking	2.0(1.4)	1.7(1.1)	1.7 (.3)

In summary, no between group differences were noted for either sleep questionnaire or log variables when subjects were grouped by level of apnea/hypopnea. Correlational procedures suggested relationships between several respiratory variables and reports of napping and wakening after sleep onset on the sleep questionnaire. These findings were cross validated in the correlational analysis of sleep log data, in which reports of napping and wakening after sleep onset were related to respiratory variables, as were total bedtime and sleep latency.

Nocturnal Respiratory and Neuropsychological Variables

Scores derived from the cognitive/neuropsychological battery included WAIS Performance IQ, WAIS Verbal IQ, Wechsler Memory Quotient, delayed recall of logical stories, delayed recall of visual reproductions, delayed recall of Rey complex figure, digit span, Hooper score, Wisconsin card sort score, finger tapping right and left, and Verbal fluency.

As a preliminary analysis, these scores were compared with selected respiratory and demographic variables in a multivariate regression procedure. In this type of analysis, a set of predictor scores is used to simultaneously predict a set of criterion variables while controlling for intercorrelations amongst the measures. An overall test of significance, such as the Hottelings T^2, establishes the probability of obtaining the observed relationships from chance alone. Upon obtaining a

significant overall p value, univariate regressions are used to individually predict criterion variables with the multiple predictors. Contribution of individual predictors may also be examined in these univariate regressions.

The results from the multivariate regression of the above noted cognitive scores and selected nocturnal respiratory variables (Apnea index, Apnea + hypopnea index, Mean high saturation, Number of desaturations $\geq 4\%$, Age, Weight:Height ratio) are presented in Table 3-13. An overall Hotellings T^2 score was significant ($p<.003$), allowing examination of the univariate regressions. Criterion variables which were significantly predicted by the respiratory and demographic variables included WAIS PIQ, WMS MQ, delayed recall of Rey figure and visual reproductions, Hooper, and Wisconsin card sort. These relationships reflected negative relationship between overnight respiratory indices and neuropsychological scores. Respiratory indices formed significant components of the predictor combinations for all these variables save Hooper score, suggesting relationships between nocturnal respiratory indices and non-verbal intelligence, verbal and visual memory, and ability to shift sets while problem solving.

Because age is correlated with nocturnal respiratory parameters in past reports, and also with neuropsychological scores in other samples, the various overnight

Table 3-13. Multivariate regression of demographic and nocturnal respiratory variables on cognitive scores in 46 snoring males.

Predictor Variables	Criterion Variables
Age	WAIS Verbal IQ
Weight:Height Ratio	WAIS Performance IQ
Apnea Index	Wechsler Memory Scale Memory Quotient
Apnea+Hypopnea Index	Delayed Recall Logical Stories
Mean High Saturation	Delayed Recall Visual Reproduction
Number of Desaturations ≥4%	Delayed Recall Rey Figure
	Digit Span
	Hooper Test
	Finger Tapping Left Hand
	Finger Tapping Right Hand
	Verbal Fluency
	Wisconsin Card Sort

Multivariate test of significance

Hotellings T^2 = 4.841 ($p<.003$)

Univariate Regression with (6,38) d.f.

Variable	Multiple R	F.	Sig.
WAIS Verbal IQ	.3646	.971	.458
WAIS Performance IQ	.5808	3.22	.012
Wechsler Memory Scale Memory Quotient	.5345	2.53	.037
Delayed Recall Logical Stories	.4713	1.80	.123
Delayed Recall Visual Reproductions	.6450	4.51	.002
Delayed Recall Rey Figure	.6461	4.54	.001
Digit Span	.2432	.39	.875
Hooper Test	.6786	5.40	.000
Finger Tapping Right Hand	.3907	1.14	.358
Finger Tapping Left Hand	.4270	1.41	.235
Verbal Fluency	.4441	1.55	.187
Wisconsin Card Sort	.5143	2.27	.050

Breakdown of significantly predicted criterion regressions

Criterion	Predictor	Beta	Sig.
WAIS Performance IQ	Age	.1240	.382
	Weight:Height Ratio	.0170	.914
	Apnea Index	-.2636	.059
	Apnea+Hypopnea Index	-.1553	.344
	Mean High Saturation	.0920	.533
	Number of Desaturations ≥4%	-.3978	.024

Table 3-13-continued.

Criterion	Predictor	Beta	Sig.
Wechsler Memory Scale Memory Quotient	Age	.0272	.852
	Weight:Height Ratio	.0996	.546
	Apnea Index	-.3315	.024
	Apnea+Hypopnea Index	-.3421	.049
	Mean High Saturation	.2384	.124
	Number of Desaturations ≥4%	-.5057	.007
Delayed Recall Visual Reproductions	Age	-.3254	.018
	Weight:Height Ratio	-.1214	.416
	Apnea Index	-.4037	.003
	Apnea+Hypopnea Index	-.2026	.191
	Mean High Saturation	.1368	.325
	Number of Desaturations ≥4%	-.2888	.078
Delayed Recall Rey Figure	Age	-.3550	.010
	Weight:Height Ratio	.1795	.231
	Apnea Index	-.2206	.091
	Apnea+Hypopnea Index	-.0572	.709
	Mean High Saturation	.3191	.025
	Number of Desaturations ≥4%	-.3228	.049
Hooper Test	Age	-.5658	.000
	Weight:Height Ratio	.1202	.403
	Apnea Index	-.1428	.251
	Apnea+Hypopnea Index	.1478	.318
	Mean High Saturation	.1072	.421
	Number of Desaturations ≥4%	-.2042	.190
Wisconsin Card Sort	Age	-.3409	.027
	Weight:Height Ratio	.0238	.887
	Apnea Index	-.3205	.031
	Apnea+Hypopnea Index	.1029	.550
	Mean High Saturation	.2383	.130
	Number of Desaturations ≥4%	-.0801	.657

scores were entered into a partial correlation matrix, controlling for age, with the cognitive scores. Table 3-14 presents the resulting correlations significant at $p<.05$ or less. The table indicates that every cognitive test but digit span and Hooper correlated with at least one overnight respiratory index. Of additional impact is the observation that in every case of a significant correlation, deteriorating respiratory indices are associated with worsening neuropsychological scores. Respiratory indices with particularly heavy loadings on neuropsychological scores included those quantifying apneas, (Apnea index, Apnea + hypopnea index) as well as those more directly representing deepening hypoxia (Mean low saturation and Number of desaturations $\geq 4\%$).

Subjects were grouped by level of nocturnal respiratory disorder (no apneas/hypopneas, subclinical level of apnea/hypopnea, and clinically significant level of apnea/hypopnea). Means and standard deviations for the neuropsychological scores from these groups are presented in Table 3-15. The table suggests a general deterioration of cognitive scores as level of nocturnal respiratory distress increases. Oneway ANOVA procedures were applied to the neuropsychological scores from each test. Significant between group differences emerged for WAIS PIQ [$F(2,43)=6.9$, $p<.002$] delayed recall of logical stores [$F[2,43)=4.0$, $p<.03$] delayed recall of visual reproductions [$F(2,43)=3.4$, $p<.04$], delayed recall of Rey complex

Table 3-14. Significant ($p<.05$) partial correlations, controlling for age, between nocturnal respiratory and cognitive variables in 46 snoring males.

	Apnea Index	Apnea/ Hypopnea Index	Event Time	Mean Saturations		Number of Desaturations	
				High	Low	≥4%	≥10%
WAIS Verbal IQ					.274	-.321	
WAIS Performance IQ	-.311	-.414*	-.421*		.521*	-.461*	-.302
Wechsler Memory Scale Memory Quotient	-.290				.251	-.311	
Delayed Recall Logical Stories	-.345					-.260	
Delayed Recall Visual Reproductions	-.416				.260	-.276	
Digit Span							
Delayed Recall Rey Figure	-.284*	-.305	-.437*	.349*	.489*	-.337	-.369*
Hooper Test	-.338			.252			
Wisconsin Card Sort		-.259			.332		
Finger Tapping Right Hand	-.258			.265	.274		
Finger Tapping Left Hand		-.364*	-.329		.365*	-.329	
Verbal Fluency							

*$p<.01$.

Table 3-15. Means and standard deviations of cognitive variables in 46 snoring males grouped by level of apnea/hypopnea.

Variable	No Apnea/ Hypopnea	Low Apnea/ Hypopnea	High Apnea/ Hypopnea
WAIS Full IQ	124.9(11.2)	118.3(13.9)	111.5 (9.6)
WAIS Verbal IQ	123.7(12)	118.5(14.5)	114.3(10.4)
WAIS Performance IQ	122.8(11.5)	114.5(14.4)	100.1(12.5)[a]
Weschler Memory Scale Memory Quotient	124.7(14.3)	117.1(19.0)	107.8(18.7)
Delayed Recall Logical Stories	9.9 (2.4)	8.6 (3.2)	5.8 (4.0)[a]
Delayed Recall Visual Reproductions	10.5 (3.7)	10.4 (3.4)	8.1 (4.7)
Digit Span	6.8 (0.8)	6.8 (1.2)	6.6 (.8)
Delayed Recall Rey Figure	25.6 (5.4)	23.2 (6.0)	15.1 (8.4)[a,b]
Hooper Test	25.2 (2.6)	25.5 (4.8)	22.8 (4.1)
Wisconsin Card Sort	4.1 (1.2)	3.4 (1.5)	2.8(1.6)
Finger Tapping Right Hand	62.6 (8.5)	57.5(10.4)	56.1 (8.3)
Finger Tapping Left Hand	59.1 (9.0)	54.0 (9.7)	54.8(13.1)
Verbal Fluency	14.6 (4.5)	13.1 (4.2)	9.3 (2.6)[a]

[a] Significantly different from no sleep apnea/hypopnea.
[b] Significantly different from low sleep apnea/hypopnea.

figure [F[2,43)=6.5, p<.003], and Verbal fluency, [F[2,43)=3.6, p<.04]. Followup comparisons (Scheffe) showed the group with high apnea/hypopnea to be significantly impaired relative to those with no sleep apnea/hypopnea on WAIS PIQ, delayed recall of logical stories and Rey complex figure as well as verbal fluency. Additionally, the high apnea/hypopnea group was impaired relative to those with subclinical apnea/hypopnea on delayed recall of the Rey complex figure. These findings are bolstered by the lack of significant between group differences on age, weight, or education (see Table 3-15), all of which are potential alternative explanations of the between group differences.

As a check, an analysis was run to evaluate the relative contribution of nocturnal respiratory variables and sleep variables reflecting fragmentation in predicting cognitive/neuropsychological scores. A multivariate regression of these scores was carried out. Demographic and respiratory scores included age, apnea index, apnea + hypopnea index, and number of desaturations $\geq$4%. A subset of the earlier noted sleep variables was chosen to reflect measures thought to be most responsive to sleep fragmentation. These included sleep efficiency, number of stage 0 periods, time % of stage 0, time % of stage 2, and number of stage changes. These respiratory and sleep parameters were used to predict the 5 cognitive scores which were earlier shown to be predicted by nocturnal

respiratory scores: WAIS PIQ, Wechsler Memory Quotient, delayed recall of visual reproductions and Rey figure, and Wisconsin card sort. Table 3-16 presents the data from this analysis. The Hotellings T^2 was significant, ($p<.001$) with delayed recall of visual reproductions and Rey figure significantly predicted by the predictor scores. Inspection of the individual regressions for these two measures discloses that age, apnea index, and number of desaturations $\geq 4\%$ all formed significant components of the prediction of delayed recall of visual reproductions, while sleep efficiency was the sole significant predictor of the Rey figure. These data seem supportive of an independent contribution of both nocturnal respiratory variables and sleep variables at a limited level, to the prediction of cognitive/neuropsychological scores.

In summary, various statistical procedures indicate relationships between nocturnal respiratory measures and non-verbal intelligence, verbal and non-verbal memory, expressive verbal fluency, and ability to shift cognitive set while problem solving. Division of subjects by level of nocturnal respiratory distress indicated that subjects with high amounts of apnea/hypopnea were impaired relative to controls on measures of non-verbal intelligence, verbal and non-verbal memory, and expressive verbal fluency, as well as being impaired relative to subjects with subclinical levels of apnea/hypopnea on measures of

Table 3-16. Multivariate regression of sleep and nocturnal respiratory on cognitive variables in 43 snoring males.

Predictor Variables	Criterion Variables
Age	WAIS Performance IQ
Apnea Index	Wechsler Memory Scale Memory Quotient
Apnea+Hypopnea Index	Delayed Recall Visual Reproduction
Number of Desaturations ≥4%	Delayed Recall Rey Figure
Sleep Efficiency	Verbal Fluency
Number Stage 0 Periods	Wisconsin Card Sort
Time % Stage 0	
Time % Stage 2	
Number of Stage Changes	

Multivariate test of significance

Hotellings T^2 = 4.063 p<.001

Univariate Regression with (9,33) d.f.

Variable	Multiple R	F.	Sig.
WAIS Performance IQ	.610	2.17	.051
Wechsler Memory Scale Memory Quotient	.566	1.73	.121
Delayed Recall Visual Reproductions	.655	2.91	.012
Delayed Recall Rey Figure	.668	2.96	.011
Verbal Fluency	.578	.85	.096
Wisconsin Card Sort	.453	.95	.499

Breakdown of significantly predicted criterion regressions

Criterion	Predictor	Beta	Sig.
Delayed Recall Visual Reproduction	Age	-.3596	.020
	Apnea Index	-.3218	.021
	Apnea+Hypopnea Index	.2329	.218
	Number of Desaturations ≥4%	-.3778	.041
	Sleep Efficiency	.2303	.408
	Number of Stage 0 Periods	.3260	.209
	Time % Stage 0	-.1136	.731
	Time % Stage 2	.0005	.998
	Number of Stage Changes	-.2235	.391

Table 3-16-continued.

Criterion	Predictor	Beta	Sig.
Delayed Recall Rey Figure	Age	-.2623	.074
	Apnea Index	-.1519	.259
	Apnea+Hypopnea Index	-.3286	.085
	Number of Desaturations >4%	-.0795	.657
	Sleep Efficiency	.6832	.018
	Number of Stage 0 Periods	.2487	.354
	Time % Stage 0	.4559	.172
	Time % Stage 2	-.0465	.802
	Number of Stage Changes	-.5054	.057

non-verbal memory. Addition of variables reflecting sleep fragmentation to the analysis indicated that both nocturnal respiratory and sleep variables make significant and independent contributions to prediction of cognitive/neuropsychological scores.

CHAPTER FOUR
DISCUSSION

Demographics and Incidence of Nocturnal Respiratory Disorder

The present sample of 46 snoring males was selecteo as a group likely to display a wide range of sleep disordered breathing. These subjects, with a mean age of 50 years and a mean weight of 190 pounds, reflect a mostly middle-aged to older male population which is moderately obese. The demographic characteristics of this sample are similar to those of the "typical" sleep apnea syndrome patient (Guilleminault et al., 1978), although the requirement of general good health insured that subjects with a classic SAS were excluded. This sample may be considered representative of subjects predisposed to sleep disordered breathing, although at no more than a subclinical level. Therefore it seems valid to consider various risk factors as they relate to nocturnal respiration.

In the present sample, 62% experienced at least one apnea or hypopnea, while 13% suffered higher levels of apnea/hypopnea. Only two other reports have described samples selected for snoring or respiratory complaints. Ancoli-Israel et al. (1981) examined 24 subjects with complaints of respiratory difficulties, daytime

sleepiness, and muscular events (nocturnal myoclonus). Further, these subjects had a mean age of almost 70 years, indicating significant sampling and age differences from the present study. Ninety-three per cent of these subjects had at least one event, while 25% had high numbers of apnea/hypopnea. These rates are much higher than those found in the present sample. This is probably attributable to the sampling differences noted above. However, a recent report by Miles and Simmons (1984) described apneas in a series of 190 patients referred for complaints of heavy snoring. In this sample, 73% had at least one event, while 9% had severe levels of apnea. These data are quite comparable to the prevalences observed in the present sample, 62% for at least one event and 13% for high levels of apnea/hypopnea, and lend some confidence to the present finding.

Thus the overall frequency of sleep disordered breathing in middle-aged subjects with heavy snoring appears to be between 62 and 73% for at least one event, and between 9 and 13% for more severe levels of apnea. The relatively close concordance of the two reports on heavy snoring subjects is reassuring.

Factors which were found to be related to the occurrence of sleep apneas in the previous review included male sex, complaints of snoring, increasing age, and obesity. The first two factors could not be examined in the present sample because of their use as selection

criteria. A wide range of age was achieved in this sample, but neither non-parametric nor correlational procedures revealed significant relationships between increasing age and sleep disordered breathing. Although several previous reports have noted relationships between increasing age and sleep disordered breathing, typically this relationship is moderate for apnea (Block et al., 1979; Carskadon et al., 1980; Bixler et al., 1982). Additionally, no other correlational data are available in subjects selected for sleep and breathing complaints. It may be speculated that the effect of snoring masks the effect of age in this group. Alternatively, some quirk of sampling may have generated this effect. Correlational procedures, however, revealed substantial relationships between weight and sleep disordered breathing. This finding is consistent with several past reports. To summarize, the present data support relationships between increasing weight and nocturnal events, while relationships between age and sleep disordered breathing are not found in this sample of heavy snoring males, perhaps because the effect of age is masked by the effect of snoring.

The temporal characteristics of the apneic events assessed by two hour interval suggested an increase in events between 3 and 5 am, although differences in sleep onset time and wakeup time render any interpretation of

these data somewhat tenuous. This finding needs replication before any conclusions may be drawn.

Ninety-eight per cent of apneic events occurred in light slow wave and REM sleep, an observation which is not surprising given that subjects spent nearly 80% of their sleep in these stages. The preponderance of events in these stages of sleep is consistent with the bulk of past reports in this area (e.g, Bixler et al., 1982; Block et al., 1979; Krieger et al., 1983).

When subjects were divided into groups by level of apnea/hypopnea, significant differences emerged on oxygen desaturation variables. Specifically, comparisons indicated that the group with a high level of apnea/hypopnea events experienced deeper desaturations than the remaining two groups. This difference occurred despite a lack of differences on age and weight among the three groups, and appears to implicate the respiratory events in the genesis of the desaturations. This is consistent with an earlier report by McGinty et al. (1982) who demonstrated that subjects with significant levels of sleep disordered breathing were impaired on oxygen desaturation variables, relative to subjects without respiratory events. Subjects with heavy snoring and multiple nocturnal apneic respiratory events appear to be at risk for nocturnal oxygen desaturation.

In summary, the present sample of 46 snoring males appears representative of those predisposed to experience

sleep disordered breathing (middle-aged, snoring males). A prevalence of 62% was observed for occurrence of at least one event, while 13% had high numbers of apnea/hypopnea, data which are consistent with an earlier report drawn from heavy snoring males. Most events occurred in light slow wave or REM sleep. No effect of age on level of sleep disordered breathing was observed, although increasing weight was linked to nocturnal respiratory events. When the sample was divided by level of apnea/hypopnea, subjects with high numbers of apnea/hypopnea suffered significantly exacerbated oxygen desaturation, although no significant differences were noted for weight or age among the groups.

Nocturnal Respiratory and Health Variables

The finding of only very limited relationships between nocturnal respiratory events and health variables must be tempered by an acknowledgement of possible bias against such findings in this sample. Specifically, the sample was selected to be normal and healthy, a criterion which undoubtably restricted the range of possible health pathology, and hence probably attenuated the correlational findings. Additionally, the self-report health checklist, the Cornell Medical Index, cannot be regarded as a powerful measure of health pathology. In a very real sense then, the odds were against finding reliable relationships between nocturnal respiratory and health variables.

In light of these caveats, it is of interest that two measures of desaturation, mean low saturation, and number of desaturations $\geq$4% were associated with increasing blood pressure readings. While a report by Guilleminault et al. (1978) noted an increasing prevalence of hypertension in subjects diagnosed with sleep apnea syndrome, a relationship between desaturation and hypertension has not been previously reported. This finding was observed in spite of the fact that subjects prescribed hypertensives were not medication free for the pressure reading.

Additionally, a check of self reports of diagnosed hypertension showed six subjects in the no event group as having diagnosed hypertension, as opposed to six in the low apnea/hypopnea group, and one in the high apnea/hypopnea group, data which did not link apnea/hypopnea, per se, with hypertension in these subjects. The isolated finding of a relationship between mean high saturation and overall number of symptoms endorsed on the CMI is more puzzling and does not follow any logical analysis.

In summary, the present study's assessment of health variables must be regarded as somewhat limited. In spite of this, an association between two measures of desaturation and a measure of blood presure was noted. It is speculated that blood presure may be more responsive to nocturnal oxygen saturation than to the apneic events alone.

Nocturnal Respiratory and Sleep/Wake Variables

EEG Data

The overnight sleep in the laboratory for these snoring subjects was noteworthy for a general shift towards lighter sleep than usual. A longer sleep latency, more awakenings, more light sleep, and less slow wave and REM sleep than normal are apparent. These findings parallel the report by Block et al. (1979) who found shifts to lighter sleep and more awakenings than in a sample of normal subjects. These changes were said to result from a first night in a strange bed and the discomfort of the multiple clips and sensors used to monitor respiration. Recording montages were identical for the present subjects, and these two factors undoubtably influenced the sleep of the present subjects as well.

An intriguing observation was a lack of covariation between respiratory and EEG sleep variables derived from the recording night. This finding is counterintuitive, as one would expect arousals from the respiratory events to influence the sleep characteristics of subjects with events. However, correlational procedures failed to support this notion. It may be that a ceiling effect was exerted on sleep measures sensitive to disturbance, one that resulted from the first night effect compounded by the discomfort of the recording procedure. The already elevated disturbance sensitive sleep variables might not

have enough free variance to respond to the respiratory events of the night. Alternatively, the EEG scoring system, which averages across 1 minute periods, might miss the short arousals and fragmentation resulting from events. Whatever the reason, the lack of covariation of sleep and respiratory measures is puzzling in light of the report of Guilleminault et al. (1978) who described arousals as a frequent concommitant of nocturnal respiratory events, although Bixler et al. (1982) failed to replicate this in a group of normal subjects.

Between group differences on the sleep variables were also absent when subjects grouped by level of respiratory distress were compared on sleep characteristics. Again it may be speculated that the effect of an exacerbated first night might obscure possible differences.

In summary, these snoring subjects appeared to achieve a night of sleep comparable to those observed in similar studies. Longer sleep latency, more awakenings, and lighter sleep were observed. Significantly, these changes characterize a first night effect (Agnew, Webb, and Williams, 1966) of lighter sleep in a strange bed, and may have been increased by the discomfort of the recording procedures. Less than a chance number of correlations were observed between nocturnal respiratory and sleep parameters. This surprising result is attributed to an exacerbated first night effect which probably functioned to obscure possible respiratory disturbed sleep parameter

correlations in this sample. Additionally, an EEG scoring system which averages across one minute periods might obscure brief sleep fragmentation from nocturnal events. Although the lack of correlation is puzzling, Bixler et al. (1982) reported similar findings. In their normal sample, few apnea induced arousals were noted. Multiple night recordings of all these parameters appear necessary to clarify the possible interaction of respiration and sleep fragmentation in a first night effect.

Daytime Sleepiness, Sleep Questionnaire, and Sleep Log Data

The three assessments of subjective aspects of sleep and sleepiness will be discussed together, as the pattern of findings lend themselves to this organization. The core finding here is a relationship between nocturnal respiratory variables and sleepiness variables manifesting itself in two forms. Daytime sleepiness, reflected in the mean SSS ratings and self report of napping on both the sleep questionnaire and logs, was positively related to various indices of nocturnal events (apnea index, apnea + hypopnea index, seconds in events, and number of desaturations). A second aspect of this relationship involved relationships between decreased saturation and reports of decreased sleep latency and nightly wakenings on the sleep logs and questionnaires.

These seemingly disparate findings may be interpreted as the sequelae of sleep disruption resulting from

disturbed nocturnal breathing. In the first case, increasing respiratory disturbance causes sleep deprivation, manifested in increased subjective sleepiness (SSS ratings) and compensatory sleeping (increased napping). The other side of this coin is a sleep pressure which causes disturbed subjects to fall asleep quickly (lowered sleep latency), and subjectively fail to report nightly wakenings, while subjects with intact respiration and hence less sleep pressure experience a longer sleep latency and awareness of nightly awakenings. Admittedly this is speculative, and two immediate problems with this formulation are evident. First, the lack of correlation between EEG sleep and respiration of the experimental night is problematic, as well as the lack of relationships between respiration and the evening "naps." However, it has already been speculated that an exaggerated first night effect obscured correlations between sleep and respiration, and it is now speculated that the two naps, at 7 and 9 pm, missed the afternoon trough of sleepiness which might have better reflected sleepiness.

The interpretation of increased sleepiness from nocturnal respiratory disturbance is useful in explaining the pattern of findings observed in this study, although some problems with this formulation were noted.

To summarize the main aspects of the discussion of sleep/wake variables, it is noted that these snoring subjects achieved a night of sleep comparable to those

reported in similar studies. A first night effect probably caused increased sleep latency, wakenings, and lighter sleep, a result which may have functioned to obscure possible relationships between sleep and respiratory variables, which were not observed. A pattern of correlations between increased respiratory disturbance and sleepiness was noted, perhaps because these variables reflected subjective reports which were largely independent of the experimental nights' sleep (SSS ratings made before sleep, sleep questionnaires reflecting trait sleep variables, and sleep logs averaged over a 7 day period following the experimental nights' sleep). Multiple night recordings appear necessary to sort out a possible synergistic interaction between the first night effect and the discomfort of the recording procedures.

Nocturnal Respiratory and Neurophysiological Variables

The major finding of the respiratory/cognitive analysis was the demonstration of relationships between nocturnal respiratory parameters and cognitive/neuropsychological scores tapping non-verbal intelligence, verbal and non-verbal memory, expressive verbal fluency, and cognitive flexibility. Most of these relationships remained when age, weight, and educational differences were ruled out as plausible alternatives.

These findings extend the boundaries set by previous work which indicated a relationship between hypoxia and neuropsychological scores. These previous reports

included Krop et al. (1973) and Krop et al. (1977), both of which noted that continuous nocturnal oxygenation treatment significantly improved neuropsychological scores in normal aged and chronic obstructive lung disease patients, respectively. The present results are also consistent with a report by Grant et al. (1982) demonstrating considerable neuropsychological impairment in chronic obstructive lung disease patients, a group known to experience hypoxia which is significantly exacerbated during sleep (Block, 1981). Additionally, West (1984) found impairments in finger tapping speed, short-term memory, and expressive verbal fluency in a group of climbers ascending Mt. Everest. Taken together, the present results and past reports present a consistent picture of relationships between both daytime and nighttime hypoxia and neuropsychological impairments.

Although the selection requirement of general good health ruled out the inclusion of subjects with a full blown sleep apnea syndrome, six of the present subjects demonstrated levels of respiratory disturbance sufficient to meet current diagnostic criteria for SAS-(A+H)I>5. These subjects showed significant impairments, relative to those with no sleep apnea/hypopnea, on measures tapping non-verbal intelligence, delayed verbal and non-verbal memory, and verbal fluency. These data are suggestive that heavy snoring males with multiple apneas/hypopneas may be at risk for cognitive sequelae. If the impairments

found in these subjects are taken as minimally comparable with subjects experiencing the classic sleep apnea syndrome, some support for the anecdotal reports of intellectual deterioretion in SAS (Guilleminault et al., 1978) is derived. However, both these conclusions stand in need of replication before they may be confidently asserted.

The mechanism underlying the link between nocturnal respiratory and cognitive variables is a fascinating enigma. To date, two explanations have been proposed as proximal causes of the changes observed in sleep apnea syndrome. The first, or "sleep fragmentation" hypothesis (Carskadon et al., 1980) notes the large number of arousals which may accompany nocturnal respiratory events and suggests that the resultant sleep fragmentation may lead to daytime impairments, particularly in the elderly. While intuitively appealing, there are several difficulties with this explanation. First, the demonstration of reliable cognitive deficits after sleep deprivation has proved surprisingly difficult (Webb, 1975). Changes in cognitive test scores such as those used in the present study have not been reliably observed following sleep deprivation. A second line of evidence inconsistent with the sleep fragmentation hypothesis is the observed lack of correlation between sleep structure and cognitive variables in normal subjects (Lerry and Webb, In press). Although this covariation has been observed in subjects

with greater physical deterioration (Feinberg et al., 1967), subjects selected for health do not display this effect. A third embarrassment for the sleep fragmentation hypothesis lies in the study of Orr et al. (1979) who described one group of symptomatic sleep apnea syndrome subjects and a group of asymptomatic snoring subjects that were matched on number of nocturnal events. Presumably, arousals resulting from events were matched in the two groups, yet the symptomatic subjects had serious impairments relative to the asymptomatic groups.

Despite these difficulties, the present study found that one of the five cognitive scores significantly predicted by the nocturnal respiratory indices was also correlated with sleep efficiency on the experimental night. However, given the earlier observed problems with the experimental nights' sleep, the inconsistent past evidence, and the limited (1) relationship observed, this finding remains inconclusive. A more ambitious study, examining sleep and respiration across several nights, is necessary to clarify this issue.

An alternative, although admittedly speculative, explanation of the cognitive changes lies in the cerebral hypoxia accompanying respiratory events. Brain dysfunction is known to occur in mild to moderate hypoxia. While the brain possess various homeostatic mechanisms to compensate for chronic hypoxia (hence the adaptation of long term residents of mountainous regions) it may be that the

multiple brief, acute desaturations experienced by the subject with apnea/hypopnea fail to activate these protective mechanisms effectively (Gibson et al., 1981). Recently, a body of evidence has accumulated which indicates that turnover of certain neurotransmitters is dramatically altered by acute hypoxia. The cholinergic synthetic pathway, which results in the formation of the neurotransmitter acetylcholine (ACh) appears to be particularly sensitive to the effects of acute hypoxia (Gibson et al., 1981). That ACh may be the neurotransmitter most affected by hypoxia of nocturnal events is provocative, in light of the "Cholinergic hypothesis" (Bartus et al., 1983) of the memory and cognitive impairment often found in aging subjects. This formulation notes that cholinergic blockade in young subjects inhibits memory, while various aspects of the cholinergic synthetic pathway are altered in aged subjects with memory and cognitive deficits. Alterations in the cholinergic synthetic pathway are thought to underlie the cognitive changes in both populations. It may be speculated that the cognitive dysfunction found in the present subjects with multiple apnea/hypopnea is also a product of a disruption of cholinergic synthesis.

To summarize the logic of the "cerebral hypoxia hypothesis," it is first noted that subjects with nocturnal respiratory events experience multiple, acute hypoxic episodes. This acute hypoxia appears to evade cerebral protective mechanisms which normally respond to chronic

hypoxia. Acute hypoxia has recently been shown to significantly alter the synthesis of ACh, a neurotransmitter implicated in memory and cognitive changes in young subjects experiencing cholinergic blockade, and older subjects experiencing age related disruption of cholinergic pathways. The hypoxic alteration of ACh turnover is proposed as the proximal cause of cognitive/memory impairments found in subjects with nocturnal respiratory events.

Although the cerebral hypoxia hypothesis is highly speculative, it does generate predictions which might be used to test its efficacy. For instance, subjects with differing levels of hypoxia might be expected to exhibit differing levels of ACh turnover, as well as cognitive differences. Administration of nocturnal oxygen should improve both cognitive and cholinergic variables. Additionally, manipulation of cholinergic pathways might improve cognition in subjects with nocturnal respiratory events. However, until a demonstration of this sort is carried out, this line of reasoning remains highly speculative.

In summary, the present findings indicate clear relationships between nocturnal respiratory and cognitive/neuropsychological variables. This result is consistent with past reports of neuropsychological impairments in subjects experiencing hypoxia. Apparently, heavy snorers with multiple apnea/hypopnea episodes may be

at risk for cognitive sequelae. These data may be taken as limited support for the anecdotal reports of cognitive changes in SAS patients. Two explanations of possible underlying mechanisms of the cognitive changes may be considered. The first, the "sleep fragmentation hypothesis," suggests that the cognitive deficits result from the multiple arousals experienced by the subject. This notion is suspect as a plausible explanation because sleep deprivation and sleep measures tapping sleep fragmentation fail to intercorrelate consistently with cognitive scores in other populations. Additionally, the extremely limited relationship observed in the present study is less than conclusive. It is proposed that cerebral hypoxia induces alterations in synthesis of ACh, a neurotransmitter implicated in cognitive abilities in other populations, and thus causes the cognitive changes. The cerebral hypoxia theory remains speculative, although several testable hypotheses may be generated from it. Further research into factors affecting the sleeping brain may prove heuristic for neuropsychologists.

CHAPTER FIVE
SUMMARY AND CONCLUSIONS

In this study, a detailed assessment of the nocturnal respiration, health status, cognitive/neuropsychological skills, and sleep/wake cycle of 46 snoring male subjects was carried out. Sixty-two per cent of these subjects experienced at least one event (apnea or hypopnea) while 13% exhibited more than 5 events per hour. Most events occurred in light slow wave or REM sleep. Obesity was linked to increasing nocturnal events. Subjects with more than 5 events per hour suffered significantly exacerbated oxygen desaturation relative to the remaining subjects. Overnight oxygen desaturation was linked to increasing blood pressure readings. As a whole, these subjects experienced a longer sleep latency, increased wakening after sleep onset, and more light sleep in the lab, the classic "first night" effect. It was thought that this first night effect obscured relationships between nocturnal respiratory and sleep parameters, which were not observed. However, overnight respiratory disturbances were linked to increased sleepiness and napping. Additionally, relationships between nocturnal events and deteriorating scores on tests tapping non-verbal intelligence, verbal and non-verbal memory, expressive verbal

fluency, and cognitive flexibility were observed. It was speculateo that hypoxic alterations in the cholinergic synthetic pathways underlayed these changes. Apparently, a significant subgroup of heavy snoring males fall on the same continuum as subjects with sleep apnea syndrome, occupying an intermediate position between normals and those with SAS. From these and other data, it is concluded that

1) between 62 and 73% of snoring males experience at least one nocturnal respiratory event, while between 9 and 13% appear to experience 5 or more events per hour;
2) most events occur in light slow wave or REM sleep;
3) increasing obesity is linked to nocturnal events in snoring males;
4) nocturnal events are linked to increasing blood pressure in snoring males;
5) nocturnal events are linked to increasing sleepiness in snoring males;
6) nocturnal events are linked to deteriorating neuropsychological scores in snoring males;
7) a subset of heavy snoring men, those with more than 5 events per hour, suffer increased oxygen desaturation and decreased cognitive abilities in the areas of non-verbal intelligence, verbal and

non-verbal memory, expressive verbal fluency, and cognitive flexibility;

8) the subset of heavy snoring males with more than 5 events per hour appear to occupy an intermediate position between normals and those with sleep apnea synorome.

APPENDIX A
SCORING PROTOCOL FOR RESPIRATORY VARIABLES

Data from the nose and mouth thermisters, as well as the oximeter and strain gauges, were used in scoring respiratory events.

An apnea was scored when a cessation of airflow at the mouth and nose lasting for 10 or more seconds was observed. Up to 3 mm of "noise" were tolerated in an apnea, as long as no rhythmic pattern which might represent shallow breathing was observed. An event began at the end of the last exhalation preceding the apnea. Duration, lowest saturation, and per cent saturation change were noted.

A hypopnea was scored when a reduction in amplitude of breathing at the mouth and nose of 50% or more was accompanied by a 10% or larger desaturation. The event began at the end of the last full exhalation. Duration, lowest saturation, and per cent saturation change were noted.

Each record was separately scored by two raters. Later each record was jointly rescored and disagreements were resolved by consensus.

A separate scoring of oxygen saturation was made by rating each minute of the record for highest and lowest saturation. Additionally, a separate tabulation of

desaturations exceeding 4 and 10% was kept. Because of the relative ease of this rating, only one rater scored saturation records.

APPENDIX B
RAW DATA TABLES

Table B-1. Demographic and medical variables from 46 snoring males.

Subj. #	Age	Education	Height (in)	Weight	Weight: Height Ratio	Blood Pressure		Cornell Medical Index			
						Diastolic	Systolic	Overall score	Respiratory	Cardio pulmonary	Neurological
1	58	12	68	250	3.67	130	090				
2	60	12	65	225	3.57	140	100	022	01	02	02
3	52	16	67	148	2.10	110	065	026	01	00	01
4	68	13	70	168	2.4	140	100	007	00	01	00
5	52	12	74	245	3.31	120	085	018	03	00	01
6	50	16	67	155	2.31	110	060	015	00	02	02
7	51	12	69	135	1.95	130	085	007	00	00	01
8	48	09	67	155	2.31	120	090	009	01	02	00
9	60	20	66	157	2.37	130	100	014	00	02	03
10	56	16	68	235	3.45	135	090	009	00	00	02
11	49	18	70	230	3.28	120	100	030	01	02	01
12	56	13	74	250	3.10	125	090	006	00	01	01
13	48	13	70	187	2.67	120	070	007	00	01	01
14	58	15	75	190	2.53	120	070	005	01	00	00
15	54	14	67	125	1.99	114	076	006	00	00	01
16	50	16	71	160	2.25	150	080	014	02	04	01
17	32	16	72	167	2.31	120	085	005	01	00	02
18	36	16	69	180	2.60	120	090	030	02	01	01
19	57	12	72	190	2.71	120	090	015	01	02	01
20	50	16	71	250	3.52	135	100	042	06	02	06
21	47	14	71	198	2.79	125	090	007	00	02	02
22	66	14	65	135	2.04	126	080	018	02	00	00
23	55	16	72	145	2.01	120	074	015	01	01	01
24	51	16	72	165	2.29	115	070	010	04	00	02
25	51	13	68	160	2.35	122	064	023	00	01	04
26	64	18	68	215	3.16	145	100	010	01	01	02
27	73	12	68	183	2.69	140	090	026	05	00	01

28	63	12	67	167	2.49	125	080	054	02	04	03
29	49	16	68	200	2.94	124	078	010	03	01	00
30	35	18	74	210	1.83	125	085	010	03	01	01
31	59	12	71	205	2.88	128	082	015	03	00	02
32	52	18	68	195	2.86	120	080	011	01	03	00
33	53	16	70	235	3.35	136	086	015	02	02	00
34	40	14	75	222	2.96	140	095	010	01	01	01
35	53	14	71	210	2.96	105	070	023	02	05	02
36	31	12	69	190	2.75	128	080	009	00	00	01
37	63	20	65	130	2.00	120	070	010	02	00	01
38	75	16	72	185	2.57	160	070	015	03	01	01
39	59	16	69	152	2.20	145	075	012	00	02	03
40	56	12	72	218	3.03	124	074	007	00	00	00
41	60	16	69	235	3.40	150	080	011	00	03	00
42	60	14	71	185	2.60	124	068	012	00	01	01
43	69	14	65	234	3.52	160	110	013	00	01	02
44	63	20	68	162	2.38	120	075	016	02	02	00
45	60	12	70	175	2.50	140	100	035	04	04	02
46	43	15	68	215	3.11	142	086	026	00	02	03

Table B-2. Daytime sleepiness variables from 46 snoring males.

Subject #	Mean Stanford Sleepiness Rating	Mean Sleep Latency - Naps	Minutes of Sleep - Naps
1	-	09.0	22
2	-	18.0	05
3	-	11.5	18
4	4.5	-	-
5	3.5	06.5	26
6	3.5	-	-
7	4.7	20.0	01
8	2.7	13.5	13
9	3.8	09.5	17
10	4.3	20.0	00
11	3.4	20.0	00
12	3.3	16.0	09
13	-	-	-
14	4.5	20.0	00
15	4.1	14.0	14
16	3.6	20.0	00
17	2.8	08.5	25
18	2.5	11.5	18
19	-	15.0	11
20	3.6	20.0	00
21	3.7	20.0	00
22	2.4	14.5	05
23	4.5	14.5	12
24	4.4	20.0	00
25	3.3	04.0	34
26	3.3	-	-
27	4.8	19.0	03
28	3.5	20.0	00
29	4.1	15.0	10
30	2.6	17.5	07
31	4.3	14.0	13
32	3.1	11.0	18
33	5.1	11.5	18
34	3.1	-	-
35	3.8	20.0	00
36	3.4	20.0	00
37	3.4	13.5	14
38	2.2	20.0	00
39	2.9	06.5	25
40	3.9	19.0	08
41	4.0	08.0	27

Table B-2-continued.

Subject #	Mean Stanford Sleepiness Rating	Mean Sleep Latency - Naps	Minutes of Sleep - Naps
42	1.5	06.0	30
43	2.5	-	-
44	3.8	03.5	35
45	3.4	-	-
46	2.1	-	-

Table B-3. Sleep questionnaire variables from 46 snoring males.

Subject #	Mean Hours Sleep	Enough ?	Number of Naps	Hours Napping	Number of Wakings	Minutes Awake	Sleep Latency	Depth of Sleep	Daytime Sleepiness
1	7	2	4	4	2	0	1	3	2
2	9	2	6	5	1	0	1	3	2
3	7	1	3	3	0	2	2	3	2
4	8	2	0	0	1	2	2	3	2
5	6	2	0	0	0	0	3	3	2
6	7	2	1	2	0	0	2	3	2
7	8	2	0	0	1	2	3	1	2
8	1	3	2	3	3	2	1	3	2
9	8	2	7	4	3	2	2	2	2
10	9	2	2	2	2	2	3	2	2
11	7	2	1	1	1	1	2	2	2
12	7	2	0	0	4	1	2	1	1
13	7	2	2	3	2	1	2	3	1
14	9	2	1	2	0	0	2	1	2
15	9	2	0	0	0	2	2	3	1
16	9	2	2	2	2	1	3	2	2
17	7	1	2	3	1	1	2	3	2
18	5	1	2	2	1	3	3	1	2
19	8	2	6	3	2	4	4	1	2
20	1	3	8	10	3	3	2	3	2
21	7	2	0	0	0	1	1	1	1
22	6	1	3	3	3	3	2	3	2
23	8	2	0	0	0	3	2	2	1
24	8	2	0	0	1	2	2	2	2

25	7	1	8	10	4	4	2	1	2
26	7	2	1	2	0	1	2	3	2
27	10	2	2	2	2	2	3	3	2
28	7	2	5	3	2	2	2	3	2
29	7	2	5	3	2	2	2	3	2
30	7	2	1	1	0	0	2	3	1
31	8	2	5	5	1	2	2	3	2
32	7	2	8	10	2	2	2	3	2
33	8	2	2	1	2	3	2	1	3
34	7	2	3	3	1	3	3	3	2
35	9	2	2	3	1	1	3	3	1
36	10	2	2	2	2	2	2	3	2
37	8	2	1	2	1	3	3	3	2
38	7	2	2	4	2	1	1	3	2
39	7	2	3	3	1	2	2	3	1
40	7	2	0	0	1	2	2	3	2
41	7	2	2	1	1	3	3	2	2
42	8	2	0	0	0	1	1	3	2
43	8	2	4	8	2	2	1	2	1
44	7	1	1	1	2	2	1	3	2
45	0	0	0	0	0	0	0	0	0
46	8	2	1	1	4	1	1	3	2

Table B-4. Seven day sleep log means from 46 snoring males.

Subject #	Daytime Sleepiness	Number of Naps	Sleep Latency	Number of Wakenings	Minutes Waking	Minutes Napping	Total Bedtime
1	2	0	3	1	2	0	7
2	2	1	5	0	1	0	9
3	2	0	15	4	2	0	6
4	2	0	7	2	3	0	8
5	3	0	12	3	2	0	6
6	3	0	16	2	1	0	6
7	-	-	-	-	-	-	-
8	3	1	9	2	2	0	7
9	2	1	21	2	4	1	7
10	3	0	19	2	3	0	9
11	3	0	6	2	2	0	8
12	-	-	-	-	-	-	-
13	3	0	9	1	1	0	7
14	2	0	17	1	1	0	9
15	-	-	-	-	-	-	-
16	3	0	12	2	3	0	9
17	-	-	-	-	-	-	-
18	2	0	35	2	3	0	7
19	2	1	30	2	5	0	7
20	2	0	7	2	2	0	7
21	3	0	14	1	2	0	9
22	2	0	14	2	4	0	7
23	3	0	9	0	1	0	8
24	-	-	-	-	-	-	-
25	1	1	5	1	2	2	5

26	2	0	16	2	1	0	7
27	2	0	15	1	2	0	8
28	5	1	5	1	2	0	8
29	2	0	4	1	2	0	7
30	3	0	8	1	2	0	7
31	2	1	7	1	2	0	9
32	2	1	13	1	1	0	7
33	2	1	31	2	2	1	8
34	-	-	-	-	-	-	-
35	2	0	11	1	2	0	9
36	2	0	17	1	1	0	9
37	1	1	22	1	3	0	8
38	3	0	7	1	3	0	7
39	2	0	5	1	3	0	7
40	3	0	16	2	2	0	8
41	2	1	18	1	4	0	8
42	3	0	5	2	2	0	7
43	-	-	-	-	-	-	-
44	2	0	13	2	4	0	10
45	2	0	6	2	2	0	7
46	-	-	-	-	-	-	-

Table B-5. Neuropsychological variables from 46 snoring males.

Subj. #	WAIS IQ Verbal	WAIS IQ Performance	WAIS IQ Full	WMS[a] MQ	DRLS[b]	DRVR[c]	Digit Span	DRRR[d]	Hooper Test	WCST[e]	Finger Tapping Right Hand	Finger Tapping Left Hand	Verbal Fluency
1	118	089	116	157	11	11	7	17	24	4	44	40	05
2	075	076	074	067	02	00	4	06	12	1	25	25	04
3	125	116	121	126	11	13	8	25	30	5	52	47	08
4	135	094	127	120	11	11	8	19	22	1	54	52	10
5	120	106	115	135	10	11	8	36	25	5	55	55	15
6	122	110	118	124	12	14	7	24	28	4	59	58	15
7	108	106	108	105	06	09	6	16	2	5	53	58	12
8	101	117	108	106	06	11	7	14	23	5	56	55	07
9	120	140	130	129	06	08	8	24	28	5	55	53	20
10	128	122	127	137	13	14	7	28	28	4	61	55	15
11	134	134	136	124	11	12	8	25	28	4	60	53	16
12	102	112	106	101	06	14	7	29	27	5	64	51	10
13	102	090	100	095	03	04	6	16	24	5	56	52	09
14	140	131	140	143	09	13	8	20	28	5	55	52	15
15	104	103	104	107	09	11	5	30	29	1	59	61	13
16	113	123	118	089	05	10	5	24	29	5	53	50	12
17	113	111	113	094	05	14	6	24	29	5	57	59	12
18	122	110	118	112	11	11	7	27	28	2	76	66	17
19	095	121	107	100	06	00	6	22	22	2	61	62	05
20	131	139	136	143	11	13	7	29	27	4	72	72	19
21	120	113	118	118	08	10	7	25	25	2	66	64	09
22	124	125	125	136	10	10	8	28	25	1	56	52	19
23	119	118	120	142	10	14	8	31	27	5	57	55	20
24	127	119	125	120	10	13	7	26	27	5	64	66	18
25	122	120	122	120	11	11	7	18	24	4	54	55	12
26	120	100	110	105	11	10	7	26	25	5	68	49	14

27	100	090	099	086	01	00	6	00	16	2	57	60	09
28	129	135	133	135	09	12	8	20	26	5	70	60	19
29	122	116	120	114	09	05	8	25	26	4	57	56	09
30	137	135	138	120	10	09	6	24	26	5	60	68	16
31	121	102	114	097	03	02	7	15	20	0	53	44	11
32	123	114	120	118	08	11	6	20	27	4	70	77	13
33	123	112	119	109	13	03	5	23	24	1	49	42	08
34	133	116	127	129	09	10	7	30	26	4	80	72	11
35	115	120	118	120	09	12	7	21	27	4	71	70	12
36	122	102	114	121	10	08	7	26	25	5	54	50	11
37	133	127	134	133	15	14	7	34	25	5	66	67	17
38	138	116	131	118	07	08	8	20	12	4	55	47	20
39	134	133	137	133	08	12	6	30	25	5	73	74	17
40	100	109	105	107	03	09	7	19	23	2	58	49	10
41	130	123	129	133	08	12	7	30	28	5	69	61	14
42	134	135	136	143	15	12	5	26	28	5	53	50	18
43	111	111	112	100	09	03	7	13	17	3	50	49	17
44	123	135	131	136	09	13	7	28	26	4	74	65	10
45	136	142	131	143	13	14	7	27	25	5	55	48	22
46	120	114	119	137	13	11	9	25	29	2	66	60	13

a WMSMQ = Wechsler Memory Scale Memory Quotient
b Delayed Recall Logical Stories
c Delayed Recall Visual Reproductions
d Delayed Recall Key Figure
e Wisconsin Card Sort

Table E-6. Respiratory variables from 46 snoring males.

Subject #	Apnea Index	Apnea+ Hypopnea Index	Seconds in Events	Mean Saturation		Number of Desaturations	
				High	Low	>4%	>10%
1	0.0	58.4	4058	93.4	80.9	220	73
2	1.7	4.2	350	93.4	88.7	214	21
3	0.5	0.5	36	94.9	93.0	26	0
4	2.5	2.5	144	96.9	94.0	74	2
5	0.4	0.9	44	95.6	92.0	123	2
6	3.4	3.7	500	95.8	91.7	90	7
7	0.2	0.2	10	95.6	91.7	5	0
8	0.0	0.0	0	95.6	94.9	0	0
9	3.6	4.8	522	98.4	95.4	145	9
10	0.5	0.5	10	95.0	94.2	2	0
11	0.0	0.0	0	91.6	90.0	22	0
12	0.3	0.9	109	95.1	92.1	148	3
13	13.0	13.0	1498	94.3	90.0	3	0
14	0.8	0.8	36	95.1	93.7	10	0
15	0.2	0.2	23	95.6	94.5	4	0
16	0.8	0.8	48	95.1	94.1	2	0
17	0.2	0.2	21	95.4	94.1	7	0
18	0.2	0.2	10	94.3	93.2	0	0
19	0.0	0.0	0	96.5	95.1	18	0
20	0.7	0.7	40	95.1	93.3	49	0
21	0.0	0.2	20	94.7	92.3	60	2
22	0.0	0.0	0	94.9	94.3	1	0
23	0.0	0.0	0	95.4	94.9	0	0
24	0.0	0.0	0	92.8	92.0	1	0

25	0.0	0.2	80	94.6	93.0	24	1
26	0.0	0.0	0	95.5	91.6	218	0
27	0.0	13.0	3192	95.7	89.0	261	74
28	0.0	4.3	441	93.6	91.5	56	21
29	2.9	5.5	514	96.8	94.4	60	19
30	0.0	0.0	0	95.1	93.3	85	1
31	11.1	12.1	1105	94.3	92.0	89	13
32	0.0	14.6	3586	95.0	87.7	226	127
33	2.7	2.7	192	94.1	91.3	99	0
34	0.0	0.0	0	96.4	95.6	4	0
35	0.0	0.0	0	96.8	95.5	10	0
36	0.0	0.0	0	97.2	96.6	4	0
37	0.0	0.0	0	97.8	97.0	5	0
38	0.8	0.8	36	96.8	95.8	11	1
39	0.0	0.0	0	97.3	95.6	84	0
40	0.0	1.8	168	98.1	95.6	74	8
41	0.0	0.0	0	95.5	94.2	16	0
42	0.0	0.0	0	95.8	95.0	9	0
43	0.0	0.0	0	91.7	90.3	48	3
44	0.0	0.0	0	96.3	95.5	6	0
45	0.0	0.0	0	96.8	96.5	1	0
46	0.0	0.2	7	94.5	92.6	57	1

Table B-7. Sleep variables from 46 snoring males.

Subj. #	TST	Sleep Latency	Sleep Efficiency	Sleep Time	Time % Stage 0	Number Stage 0 Periods	Time % Stage					% Slow Wave Sleep	Number Stage Changes	REM Latency	Mean REM	REM Cycle
							1	REM	2	3	4					
1	506	9	0.6	185	38.4	5	1.7	0	60.6	0	0	0	14	0	0	0
2	373	5	0.6	210	12.9	8	5.8	0	71.0	9.9	0.4	11.9	51	0	0	0
3	401	0	6.9	384	4.2	10	5.9	17.9	48.3	8.7	16.5	26.3	65	82	18	90.7
4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5	374	8	0.7	283	22.6	12.0	3.6	10.9	46.5	4.9	11.5	21.2	52	75	20	255.0
6	487	2	0.9	458	5.6	8	5.9	16.2	55.5	2.9	15.8	19.5	47	72	15	86.3
7	491	18	0.9	371	10.1	14	5.3	16.2	69.9	2.1	1.7	4.3	64	165	15	61.8
8	396	14	0.7	283	25.1	9	3.2	12.6	63.8	1.8	0.5	3.1	38	190	25.5	88.0
9	468	54	0.6	383	7.5	2	1.9	25.4	47.5	6.1	11.8	19.3	36	36	26.3	119.7
10	395	94	0.3	110	57.8	3	1.9	1.5	26.8	1.9	9.9	28.1	16	221	4	0
11	407	30	0.8	341	9.3	7	2.1	21.8	65.4	2.7	1.6	4.7	42	68	27	145
12	402	154	0.5	199	9.9	6	1.4	0	87.8	0	0	0	16	0	0	0
13	399	50	0.7	267	23.5	7	3.7	2.9	60.5	2.6	6.9	12.3	30	247	5	49
14	358	135	0.6	205	8.1	9	0.5	17.0	65.5	4.5	4.5	9.8	32	82	19	167.0
15	382	34	0.8	335	3.7	7	0.3	17.0	59.2	4.3	15.5	20.6	29	212	29.5	106.0
16	358	59	0.6	219	26.8	10	2.0	2.6	62.5	6.0	0.0	8.2	44	292	8	0
17	374	25	0.8	306	1.5	2	0.9	17.1	66.5	4.5	9.7	14.4	21	97	26.5	120
18	343	11	0.9	320	5.6	7	2.7	18.1	53.6	2.1	19.9	22.8	30	71	15	75.7
19	329	24	0.2	73	55.8	2	1.9	0	41.7	2.5	0	5.4	11	0	0	0
20	448	67	0.7	321	13.7	7	4.0	16.7	57.3	2.9	7.5	12.1	40	135	31	122
21	325	17	0.7	236	15.1	9	1.1	14.0	52.5	7.5	9.7	20.1	45	151	19.5	114
22	348	9	0.8	280	17.4	7	3.9	7.9	53.9	2.3	14.5	20.4	32	87	13.5	178
23	284	6	0.9	268	3.3	4	1.8	9.8	67.2	6.9	13.7	21.3	34	114	13.5	95
24	378	19	0.8	290	19.2	12	2.8	8.9	61.5	2.2	5.0	9.6	39	291	32	0
25	326	0	0.9	285	7.5	12	2.3	21.1	60.4	2.6	7.1	10.5	44	43	10.8	47.6
26	356	23	0.6	221	33.6	33	2.1	0	64.3	0	0	0	71	0	0	0
27	364	28	0.6	232	20.5	18	6.9	9.6	63	0	0	0	58	262	28	0
28	327	19	0.8	265	4.3	4	2.9	13	66.4	4.7	8.7	13.9	30	81	9	64
29	344	6	0.8	273	19.2	11	2.7	15.9	62.1	0	0	0	32	153	18	58.5
30	340	20	0.9	295	7.8	6	3.1	15	63.4	4.7	6	3.1	38	65	16	111
31	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

32	393	5	0.8	372	5.1	5	2.6	16.9	66.9	5.2	11.2	16.9	40	70	16.5	100.7
33	429	2	0.9	377	11.1	8	1.6	8.3	83.3	0.7	5.1	4.2	27	102	1	0
34	378	33	0.7	264	20	10	15.6	10.0	59.7	1.2	5.3	5.7	37	87	11	106
35	355	51	0.7	240	21.6	6	1.3	1.3	69.1	1.6	5.6	9.2	23	9298	2	5
36	321	26	0.9	284	2.7	4	5.8	10.6	55.1	3.1	20.4	30.3	29	147	15.5	105
37	424	28	0.8	359	8.9	9	2.5	9.9	75.1	1.0	5.3	6.9	35	109	13	133
38	323	21	0.7	221	9.4	7	1.6	14.8	63.9	4.9	5.3	11.3	30	127	18	55
39	416	5	0.9	385	6.3	7	2.2	10.7	67.2	1.9	15.6	16.6	37	177	14.7	98
40	372	41	0.8	319	0.5	10	5.2	23.5	59.5	2.4	7.9	10.9	40	91	26.7	88
41	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
42	356	1	0.9	334	5.7	11	11.5	12.4	61.7	5.2	7.5	11.1	12.4	61.7	10.8	72
43	442	28	0.8	352	8.8	6	5.6	15.5	47.9	7.5	19.2	28.9	56	113	20	125.5
44	429	5	0.9	375	9.6	5	2.9	10.6	64.8	2.4	8.9	12.5	40	95	17.5	85.7
45	434	22	0.7	328	20.4	23	5.6	5.4	60.2	5.4	7.0	13.1	70	393	7	17
46	570	54	0.8	505	2.8	6	0.6	16.7	65.1	5.5	11.2	17.2	29	125	26	159

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I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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Graduate Research Professor of Psychology

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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